The impact of cannabis use and polygenic risk scores on symptom dimension profiles at psychosis onset

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The Impact of Cannabis Use and Polygenic Risk Scores on Symptom Dimension Profiles at Psychosis Onset

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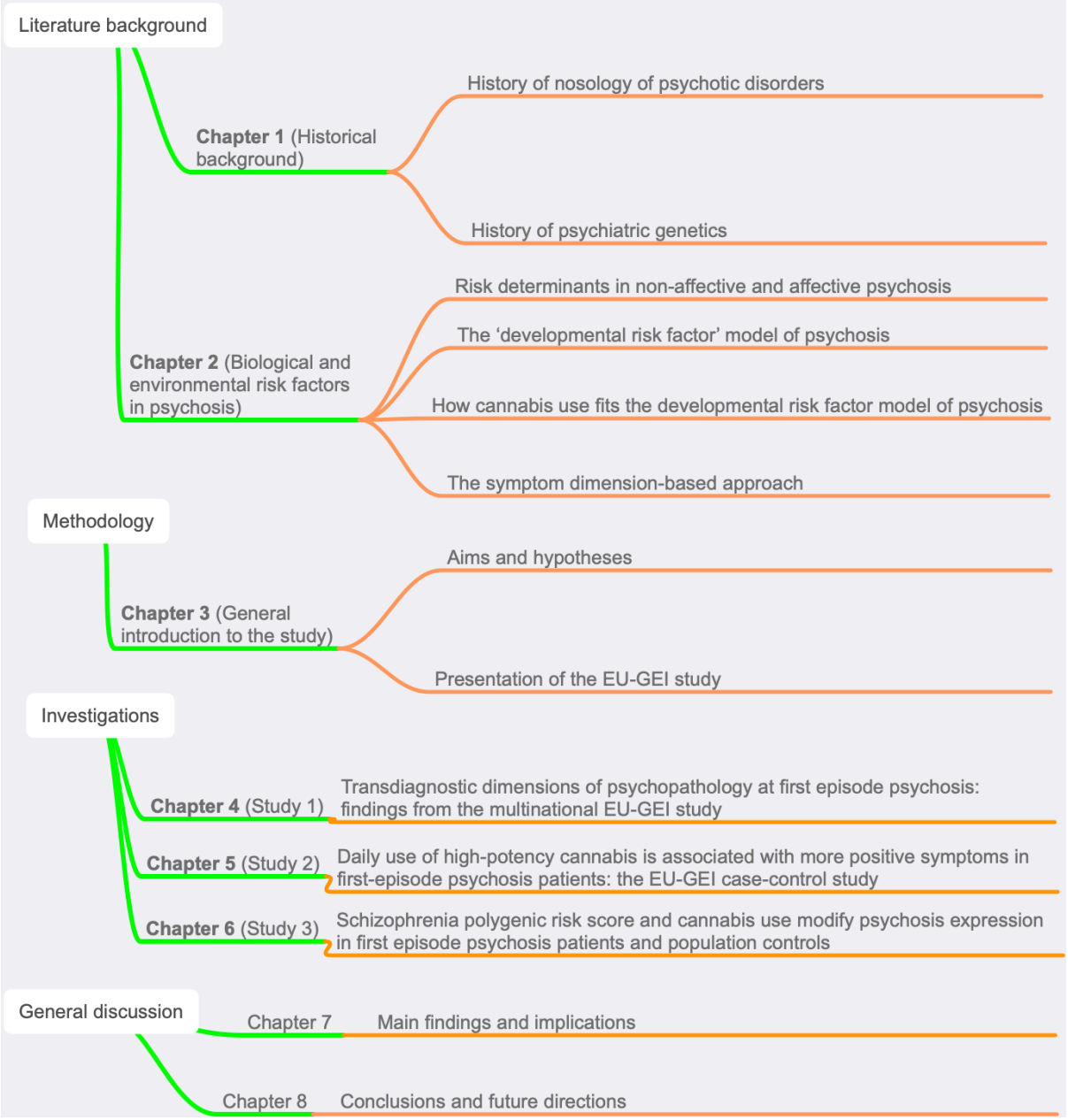
Finally, a few verses, that may sound unusual to many but familiar to some, reflect my many, many nights spent at the Institute of Psychiatry - the place which has been the North Star whilst I have sailed my research journey.

There is a place
At the edge of time,
at the centre of the universe
Where you can gather
in the solitude of an infinite crown.
Oh, tiny shrine,
you have the celestial vault as a sky
And walls that are billions of years away,
and immense, like your floor
which is covered by a minuscule seed

Organization of the thesis

This thesis comprises eight chapters, each of them including a brief introduction. Chapters 1 and 2 present (a) the longstanding debate on nosology of psychotic disorders; (b) current understanding of biological and environmental risk factors for non-affective and affective psychoses, focusing on common genetic variants and cannabis use; (c) the integration of these risk determinants into a developmental risk factor model of psychosis; and (d) the symptom dimension based approach toward conducting transdiagnostic research into this model. Chapter 3 illustrates general aims and hypotheses of this thesis, introducing the European Network of National Schizophrenia Networks studying Gene-Environment Interactions' (EU-GEI) study. In chapters 4, 5 and 6, the experimental part of this thesis is presented, in the form of two published and a submitted paper. A general discussion is presented in Chapter 7, and conclusions and future directions in Chapter 8. A diagram summarising the organization of the thesis is shown below.

Figure 1. Diagram of the organization of the thesis.



Abstract

Introduction

Epidemiological and biological evidence show no boundaries between diagnostic categories of non-affective and affective psychoses, thus challenging the current nosological model developed from Kraepelin's paradigm. My thesis aimed to address this limitation by 1) examining the transdiagnostic dimensional structure of i) psychotic symptoms in first episode psychosis (FEP) patients and ii) psychotic experiences in the general population; 2) investigating the relationship between these dimensions and a set of external factors, such as the use of cannabis and genetic common variant liability for psychotic disorders. Overall, I expected that differences in symptom profiles at FEP reflected gradients of neurodevelopmental impairment in psychosis.

Methods

This thesis uses data from a multisite incidence and case-control study, which I worked on, conducted across six countries [i.e. the 'European Network of National Schizophrenia Networks studying Gene-Environment Interactions' (EU-GEI) study]. To examine the latent structure of psychopathology, I analysed ratings of psychotic symptoms and experiences using multidimensional item response modelling in M*plus*, and I estimated different theory-based models of psychosis, including unidimensional, multidimensional, bifactor, and hierarchical solutions. To examine the common variant liability to psychosis, I examined the population structure in the EU-GEI sample and computed ancestry-specific schizophrenia (SZ), bipolar disorder

(BP), and combined schizophrenia-bipolar disorder (SZ-BP) Polygenic Risk Scores (PRSs) in PRSice.

To examine the relationship between the latent structure of psychopathology and demographic and context determinants, detailed patterns of cannabis consumption, and PRSs, I used multiple linear regression models fitted in STATA14.

Results

The associations among ratings of both psychotic symptoms in FEP patients and psychotic experiences in population-based controls were best represented by a bifactor model, composed of one general psychosis factor and multiple specific dimensions. In FEP patients, the examination of general and specific dimensions with external factors showed that 1) higher scores on the negative symptom dimension were associated with being a male, and having never used cannabis; 2) higher scores on the positive symptom dimension were associated with exposure to socioenvironmental risk factors in psychosis, such as being part of an ethnic minority, and having had exposure to cannabis in a dose-response fashion, with those having used high potency varieties on a daily basis having the highest score; 3) both higher scores on the positive and negative symptom dimensions were associated with a higher SZ-PRS.

In population-based controls, the examination of general and specific dimensions with external factors showed that 1) higher scores on the positive psychotic experience dimension were associated with current use of cannabis but not with the extent of lifetime exposure to cannabis; 2) higher scores on the general and all the specific psychotic experience dimensions were associated with a high SZ-PRS.

Conclusions

My thesis shows that symptom dimensions are useful psychosis phenotypes, that are validated by psychometric data and socioenvironmental and genetic factors. Specifically, the bifactor model of psychopathology holds across diagnostic categories of non-affective and affective psychosis at FEP and in the general population. Furthermore, my findings indicate that use of cannabis is associated with more positive and less negative symptoms at FEP, consistently with the hypothesis that cannabis users who develop psychosis have less early neurodevelopmental impairment than their non-user counterparts. Overall, these findings indicate that it is appropriate to conduct research using enhanced phenotypes, and they have translational relevance, they are important for developing secondary prevention strategies in psychosis. Currently, symptom dimensions at FEP could be used for formulating clinical impressions regardless of diagnostic categories according to a developmental-symptom approach, and for guiding tailored treatments.

Statement of Contribution

Except where indicated the work submitted is the result of my own investigation and the views expressed are mine. The papers presented in Chapter 3, 4, and 5 include data from Work Package 2 (WP2) of the EU-GEI study, collected by a multinational research team before my PhD started. Biological samples of the study participants were genotyped at the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff (UK). Overall, I contributed to the WP2 EU-GEI study by: 1) data cleaning for all the study sites; 2) recovering missing data through access to clinical records where possible; 3) rating psychopathology through clinical records for most cases

recruited in London; 4) collecting additional biological samples in London as substitutes for those which failed initial quality control; 5) building and through the management of the central database integrating biological data with phenotype information; 6) computing principal ancestry components and polygenic risk scores (PRSs) as shown in the papers; 7) leading the follow-up study on the London sub-sample, to be used as the basis for future development of the findings in my thesis.

Table of contents

Chapter 1. History of nosology of psychotic disorders and psychiatric genetics

In this chapter, I present the key milestones in the history of nosology for psychotic disorders and for psychiatric genetics. In the first part of the chapter, I illustrate the methodological caveats and dissatisfaction on the categorical distinction between non-affective and affective psychoses which were expressed since the inception of this dichotomy, and that ended up driving research and clinical practice. The second part of the chapter covers a brief history of psychiatric genetics. I explain how recent collaborative efforts provide an improved insight into the genetics of psychotic disorders and allow individuals to be indexed according to their genetic susceptibility to these disorders.

1.1 Historical evolution of the concept of psychosis

The concept of psychosis was introduced in psychiatric literature in the 19th century, initially as a synonym for 'insanity' or 'mental illness' (Canstatt, 1843), which was linked to a hypothetic neuro-biological basis (Friedreich, 1836). Since then, three main theoretical distinctions have refined the concept of psychosis.

1.1.1 Exogenous and endogenous psychosis

The first main conceptual distinction was made between endogenous and exogenous psychosis, as proposed by the French and German schools of thought. For example, Jacques-Joseph Moreau de Tours, who may be considered an early pioneer of current experimental studies on cannabis, used the intoxication states at the *Club des Haschischins* in Paris as an exogenous model for studying psychosis (Moreau de Tours, 1845); Paul Julius Möbius later distinguished endogenous from

exogenous psychosis based on possible etiological factors, attributing endogenous forms to hereditary-degenerative causes (Möbius, 1892). Shortly after, Karl Bonhoeffer established the fundamental framework of exogenous psychosis, introducing the concept of exogenous reaction types. Bonhoeffer hypothesised that different physical conditions could result in similar psychotic syndromes, so that the symptoms that we observe would be nosologically unspecific (Bonhoeffer, 1908, 1917).

1.1.2 Kraepelin's paradigm of non-affective and affective psychotic disorders

A second fundamental distinction in psychiatric nosology was made by Emil Kraepelin, who subdivided the endogenous psychosis into dementia praecox and manic-depressive insanity (Kraepelin, 1899). This dichotomy was extremely influential, to the point that current diagnostic distinction between non-affective and affective psychotic disorders is often referred as the Kraepelin's paradigm, since it is mostly based on the differences between dementia praecox and manic-depressive insanity. Moreover, coherently with the German phenomenological tradition, Kraepelin postulated that psychosis had a causal explanation. More specifically, he assumed that dementia praecox and manic-depressive insanity were precise 'natural disease entities' ('natürliche Krankheitseinheit'), on which several external validators should have converged. This theory was by and large consistent with Karl Kahlbaum's original notion of a strict correspondence between hebephrenia and aetiological factors, symptomatology and outcome (Kalhbaum, 1863). However, according to Kraepelin, there was a gradient of importance of these 'validators' in distinguishing dementia praecox from manic-depressive insanity, with the highest importance attributed to the course and outcome of the disease (Kraepelin, 1899).

Unfortunately, Kraepelin went on to attribute a pessimistic connotation to dementia praecox: "*The common outcome of all severe forms of dementia praecox is dementia. . .The prognosis of manic-depressive insanity is favourable for the individual attack. . .even after very long duration of excitement or depression, one may still hope with great probability for complete restoration.*" (Kraepelin, 1899). Notably, psychiatrists often ignore that Kraepelin amended several times his nosology (e.g., his textbook had nine editions, from 1899 to 1927), as he was receptive to new empirical data and contemporary criticisms. For example, he accepted Bonhoeffer's theory that psychopathology may be nosological unspecific, and, in 1921, Kraepelin even came to doubt his own paradigm, acknowledging the existence of a group of patients with prominent affective and psychotic symptoms, who were not classifiable (Kraepelin, 1921). Indeed, the term schizoaffective psychosis, introduced by Jacob Kasanin in 1933, served to categorise these patients (Kasanin, 1933) and it reflected the absence of a neat distinction between affective and psychosis spectra in clinical practice. Throughout his career Kraepelin continued to believe in natural disease entities, despite many psychiatrists strongly argued that their existence could not be proven using the resources available at the time (Hoche, 1912).

The term schizophrenia was first mentioned by Eugen Bleuler in 1908, and published in the chapter "Dementia praecox and the group of schizophrenias" (Bleuler, 1911). Bleuler was concerned to understand the common characteristics across schizophrenias, eventually conceptualising the core of the disease as being composed of "*four As*" (i.e., *Association* (lack of), *Affectivity*, *Ambivalence*, and *Autism*). Enlarging the concept of schizophrenia into a heterogenous group of schizophrenias was coherent with Bleuler's strong therapeutic attitude, to the point

that, in contrast with Kraepelin's fatalistic concept of dementia praecox, Bleuler reported individuals with a full recovery from schizophrenias (Maatz *et al.*, 2015). Unfortunately, it was Kraepelin's nihilistic attitude towards dementia praecox which survived across time and was applied to the term schizophrenia, despite the fact that, currently, some maintain that only a small proportion of patients do not recover if they are properly treated (Guloksuz and van Os, 2018).

1.1.3 Psychosis and neurosis

The evolution of the concept of psychosis and the introduction of psychoanalysis at the end of the 19th century led to a third main conceptual distinction in the modern nosology, which was made between 'neurosis' and 'psychosis' (Burgy, 2008). Karl Jaspers and the Heidelberg phenomenological school enforced this diagnostic distinction, highlighting that neurosis was a psychological development process, which allowed psychological comprehension, whereas psychosis was the result of a somatic illness, which required a causal explanation and was not otherwise comprehensible (Jaspers, 1913). The work of the Heidelberg school, as extended by Kurt Schneider and later continued by Walter Ritter von Baeyer, resulted in a progressive hierarchization of diagnoses, so that '*psychopathic-neurotic'* and *'depressive-manic'* were considered to be less biologically driven than *'schizophrenic'* and *'psycho-organic'* (Schneider, 1931). Thus, according to the Heidelberg school, psychotic symptoms were indicative of biological aetiology, while the speculative and ideological character of psychoanalytic theory was gradually criticised (Burgy, 2008).

1.2 The operational revolution

Currently, the two main classification systems in psychiatry (i.e., International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM)) define diseases based on the presence of specific diagnostic criteria. The introduction of these criteria was considered a revolution in psychiatry that occurred in the context of the '*operationalism'*, a methodological framework used for defining phenomena that are not directly observable. This approach was first adopted in physics by Percy Bridgman, and it served as a pragmatic way to reduce metaphysical assumptions over the scientific progress (Bridgman, 1927). The operationalism was widely discussed among psychologists since the 1930s (Stevens, 1935, Waters and Pennington, 1938, Bergmann and Spence, 1941); and it was comprehensively presented to psychiatrists in 1959 at the introductory lecture of the American Psychopathological Association conference, which was given by Carl Hempel, a logical positivist not involved in mental health research (Zubin, 1961). Shortly after, Erwin Stengel, an expert in classification systems who served as the discussant at the Hempel's lecture and had been already concerned with the application of operationalism (Stengel, 1958), proposed the introduction of operational definitions to the World Health Organization (WHO) for revising the psychiatric section of the ICD (Stengel, 1959). Although Hempel was not involved in the subsequent construction of modern psychiatry nosology, some authors point out that Hempel's lecture had an important and direct effect on the construction of DSM-III (Bolton, 2008, Parnas and Bovet, 2015), whereas others claim that the new classification followed an ongoing operationalism revolution and was largely independent from Hempel's contribution (Aragona, 2013a, b, Cooper and Blashfield, 2018). Moreover, other experts acknowledge that Hempel's paper '*Introduction to the*

Problems of Taxonomy', published in the conference proceeding (Zubin, 1961), impacted American nosology through the work of British psychiatrists such as Sir Aubrey Lewis at the Institute of Psychiatry (Sartorius and Norman, 2009, Cooper and Blashfield, 2018). Indeed, Lewis had been concerned with differences in the definition of schizophrenia and in evaluating treatments across Europe since 1937 (Lewis, 2003, Cooper and Blashfield, 2018). The transcripts of the discussion during Hempel's lecture at the conference indicate that Lewis strongly sustained that any psychiatry theory at that time would have not been solid enough and therefore: *(LEWIS) "…for the purpose of public classification we should eschew categories based on theoretical concepts and restrict ourselves to the operational, descriptive classification…*" (Zubin, 1961).

Based on these principles and on a descriptive symptom-based approach, Lewis and colleagues generated "A Glossary of Mental Disorder" (Registrar General's Advisory Committee on Medical Nomenclature Statistics Sub-Committee on Classification of Mental Disorders, 1968). Moreover, most of these principles were reiterated in the subsequent "Glossary of Mental Health Disorders and Guide to their Classification of Mental Disorder", which was written by a WHO committee directed by Lewis (World Health Organization, 1974).

It is noteworthy that, following the conference, a group of American and British psychiatrists (e.g. Aubrey Lewis, Paul Hoch, Morton Kramer, Benjamin Pasamanick, Joseph Zubin, J.K. Wing, Robert Spitzer and Robert Kendell) joined the 'US-UK Diagnostic Project' from 1966 to 1971, to examine the differences in diagnostic frequencies across these two countries. They found major discrepancies in the schizophrenia, which was, for example, diagnosed at higher frequency in New York than in London, mainly due to different diagnostic practices of psychiatrists (Cooper

and et al., 1972). It became clear that the American concept of schizophrenia was broader than the British one. Interestingly, both American (Spitzer *et al.*, 1964) and British (Wing *et al.*, 1967) symptom rating scales were used for this project, and J.K. Wing and Robert Spitzer went on to develop computer software to turn a list of symptoms into a specific diagnosis, such as CATEGO (Wing *et al.*, 1974) and DIAGNO (Spitzer and Endicott, 1969). Finally, the contribution of Robert Kendell to the US-UK project was highly relevant, given his expertise in statistical approaches (e.g. factor analysis) and his Popperian identification of the *essential* characteristics for each diagnosis (Cooper and Blashfield, 2018). Indeed, Spitzer had a high regard for Kendell's '*The Role of Diagnosis in Psychiatry*' (Kendell, 1975, Spitzer, 1977), which may be considered a milestone in the nosology development process.

Furthermore, American psychiatry was radically changing at the time of operationalism, as evident by the different scenarios met by Michael Shepherd in 1957 and Robin Murray in 1979 during their respective travel fellowships in US. These differences included a progressive decline of psychoanalysis in favour of behavioural psychotherapy, and an increased focus on neuropsychopharmacology and biological psychiatry (Murray, 1979). Indeed, in the 1970s, a group of psychiatrists at the Washington University School of Medicine in St. Louis, self-called neo-Kraepelinians, were challenging the psychosocial model of psychiatry common in the US, with the aim to identify biological substrates of psychiatric diseases and "*carving the nature at his joints*". These efforts culminated with the publication of Feigner's criteria (Feighner *et al.*, 1972).

Feigner's criteria were subsequently modified by Spitzer as Research Diagnostic Criteria (RDC) (Spitzer *et al.*, 1978); indeed, both these criteria were designed for research purposes (e.g. by prioritising the exclusion of false negatives over the inclusion of false positives).

Since Spitzer became the head of the Task Force on nomenclature and Statistics at the APA, the development of DSM-III (American Psychiatric Association, 1980) was due to the fusion of the neo-Kraepelinian conceptualization with the operationalized project. Moreover, this process was highly influenced by British psychiatrists and possibly by the WHO Glossary, as Spitzer had reviewed it for publication in the American Journal of Psychiatry (Cooper and Blashfield, 2018). Also, having actively participated to the US-UK project, Spitzer had a strong knowledge of psychiatry in the UK.

Finally, after the publication of the ICD-10 (World Health Organization, 1992), the use of operationalised criteria became popular in clinical practice in Europe and in the rest of the world, as well as in US.

In summary, the operationalised principles that guided the US-UK 'operationalised' task force required that: 1) aetiology should be excluded as a classificatory principle since unknown; 2) diagnostic criteria should be based upon easily observable features; 3) diagnoses should reflect narrow, rather than broad, disorders; 4) 'psychosis' and 'neurosis' should not be included as classificatory principles.

1.2.1 Some unforeseen consequences of operationalism: the decline of phenomenology

The two major exclusions from the DSM-III pragmatic principles were aetiology (since unknown), and phenomenology (e.g., the examination of the individual's subjective experience). Excluding phenomenology aimed to make the rating of signs and symptoms as easy as objective. This was due to the fact that operationalised criteria were originally thought to be a pragmatic supplement to the narrative definitions of diagnostic criteria: that is, clinicians were free to ignore them and formulate diagnosis based on their clinical judgement (Spitzer *et al.*, 1978), including any identification of phenomenal Gestalts of the psychopathology experience. However, this precaution did not survive to the DSM-III publication, despite the fact that the logical empiricism used for operationalised classifications was too reductionist to disentangle complex psychopathology phenomena (Faust and Miner, 1986).

Forty years after the introduction of the DSM-III and its updates (DSM-IV and DSM-5), and in the context of the approval of the updated ICD-11 by the World Health Assembly in May 2019, many scholars became worried about a serious crisis of confidence in psychiatry nosology (Zachar and Kendler, 2017).
Nancy Andreasen, an eminent member of the Task Force on the DSM-III, went to claim that DSM led to the 'death of phenomenology' and dehumanised the practice of psychiatry (Andreasen, 2007). Of note, Robin Murray had cautiously warned about these risks as early as in 1979, "*…these [DSM-III] criteria may not be employed to the fullest advantage because many American psychiatrists are not familiar with systematic examination and recording of the mental state. German*

phenomenological psychiatry, so influential elsewhere, never took root in North America. Consequently, even in the most research-oriented centres, the attempt to diagnose according to strictly defined conventions founders at times on an inability to elicit mental phenomena accurately" (Murray, 1979). Moreover, post-operationalised psychiatric trainees began to ignore descriptive psychopathology and phenomenology (Andreasen, 2007), whilst formulating somewhat dogmatic diagnoses.

Indeed, DSM is sometimes referred to as the 'bible of psychiatry' (Paris and Phillips, 2013) and often considered unshakably valid. After its introduction, symptoms began to be identified as an isolated entity, existing independently from the patient's Gestalts of altered experience; and diagnoses began to have an independent existence of their own. Steven Hyman defined this effect as 'reification' of psychiatric disorders, due to the widespread acceptance of DSM, despite the fact that DSM was supposed to be only a heuristic and provisional proposal (Hyman, 2010).

1.3 Psychotic disorders in DSM-5 and ICD-11

Currently, psychotic disorders are generally divided into organic and functional psychosis. Organic psychosis is due to a specific medical condition (for example, neurological disorders or structural brain abnormalities), whereas functional psychosis is thought to be caused by multiple genetic and socioenvironmental factors.

Moreover, functional psychosis is commonly subdivided into non-affective and affective psychotic disorders. DSM-5 includes non-affective disorders in the chapter 'Schizophrenia spectrum and other psychotic disorders' (American Psychiatric

Association, 2013), defining eight types of discrete functional conditions (codes in brackets), such as: Delusional Disorder (297.1); Brief Psychotic Disorder (298.8); Schizophreniform Disorder (295.40); Schizophrenia (295.90); Schizoaffective disorder (295.70); Substance/Medication induced psychotic disorder (291.xx or 292.xx based on the substance of abuse); catatonia (293.89). In addition, DSM-5 considers schizotypal personality as part of the schizophrenia spectrum, although it is described in the chapter "Personality Disorders".

On the other hand, affective psychotic disorders are included in the chapter of 'Bipolar and Related Disorder', and in the chapter of 'Depressive Disorder', with a specifier indicating psychotic features (i.e., Bipolar disorder / Major Depression with mood-congruent psychotic features (); and Bipolar disorder / Major Depression with mood-incongruent psychotic features).

ICD-11 was approved by the World Health Assembly in May 2019 and it will be used by the WHO member states from 2022. ICD-11 "*Schizophrenia and other primary psychotic disorders*" include all conditions where psychotic symptoms are a core aspect, as opposed to conditions (e.g., mood disorders) where psychotic symptoms may be secondary to other forms of psychopathology. Similarly to the transition from DSM-IV to DSM-5, also in the transition from ICD-10 to ICD-11 symptoms of schizophrenia have remained largely unchanged, however first-rank symptoms have been de-emphasised and subtypes of schizophrenia have been replaced by dimensional descriptors [e.g., positive symptoms (delusions, hallucinations, disorganized thinking and behaviour, experiences of passivity and control); negative symptoms (constricted, blunted or flat affect, alogia or paucity of speech, avolition, anhedonia); depressive mood symptoms; manic mood symptoms; psychomotor symptoms (psychomotor agitation, psychomotor retardation, catatonic symptoms);

and cognitive symptoms (deficits in speed of processing, attention/concentration, orientation, judgment, abstraction, verbal or visual learning, and working memory)] (Reed *et al.*, 2019).

The main difference between DSM-5 and ICD-11 is related to the diagnosis of Schizoaffective Disorder, which in DSM-5 relies on the longitudinal course of the disease, whereas in ICD-11 schizoaffective disorder is diagnosed based on schizophrenia symptoms in concurrence or within a few days of a manic or depressive episode (psychotic and mood symptoms should last > 4 weeks) (Gaebel *et al.*, 2012). Although this approach aimed to improve the diagnostic agreement, which is known to be low for schizoaffective disorder, first trials showed that these modifications in ICD-11 resulted only in a tiny improvement compared with previous ICD-10 (Peterson *et al.*, 2019).

1.3.1 Psychotic disorders' main features

Briefly, according to DSM-5 and ICD-11, in order to make a diagnosis of psychotic disorders, five main features should be taken into consideration: delusions; hallucinations; disorganized thinking (speech); grossly disorganised or abnormal motor behaviour (including catatonia); negative symptoms.

Delusions

Delusions are fixed beliefs which are not modifiable by convergent contradicting evidence regarding their veracity (American Psychiatric Association, 2013). Their content may refer to several themes, for example ranging from persecutory and referential delusions to somatic, religious, nihilistic, and grandiose delusions. Delusions are considered bizarre when their content is not understandable in the

same peer cultural context, and they do not therefore derive from ordinary life experience. Delusions of control or passivity phenomena are also considered bizarre, and they are commonly considered particularly pathognomonic of schizophrenia, i.e. first-rank symptoms of schizophrenia (Schneider, 1959).

Hallucinations

The first medical understanding of hallucinations was of a 'percept without an object', which was more linked to the conviction of the truth of their experience rather than to sensory disturbance (Esquirol, 1838). To exclude from this definition physiological conditions such as dreams, Jaspers considered these false perceptions should occur at the same time as the real perception (Jaspers, 1913). This phenomenological concept of hallucinations has persisted into the modern diagnostic criteria and has served as the basis for contemporary research. For example, within the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) conceptual framework, hallucinations are considered as conscious sensory experiences occurring without corresponding external stimulation of the sense organ and resembling a veridical perception (Ford *et al.*, 2014b). Empirical studies have shown that hallucinations involve at a neural level the circuits from cochlear neurons to the superior temporal gyrus, and at a cognitive level the whole perceptual system including integration of different perceptions and cross-modal integration (Aleman and Larøi, 2008, Ford *et al.*, 2014a, Parnas and Kendler, 2017).

Hallucinations are central to the psychopathology of psychotic disorders (American Psychiatric Association, 2013), and certain types were for many years regarded as first rank symptoms of schizophrenia (Schneider, 1959).

Disorganised thinking or speech

A formal thought disturbance in the form of disorganised thinking can be evident, for example, when the answers provided are unrelated to the questions (tangentiality), or when there is a sudden switching from one topic to another (derailment) (American Psychiatric Association, 2013). Disorganization may also relate to the language domain (Goldberg and Weinberger, 2010), for example speech may be incomprehensible, due to incoherence or “word salad”.

Grossly disorganised or abnormal behaviour

Although a wide range of abnormal behaviours is observed in psychosis, one common characteristic could be often summarised as a deficit of goal-directed behaviour, e.g., resulting in a reduced ability to plan or perform activities (American Psychiatric Association, 2013).

Moreover, DSM-5 indicates catatonia as an abnormal behaviour, which may present in different forms, such as resistance to instruction (*negativism*), maintaining a rigid or bizarre posture (*catalepsy*), or lack of verbal (*mutism*) and motor (*stupor*) responses (American Psychiatric Association, 2013).

Negative symptoms

“Negative” symptoms signify a function that is dysfunctional as diminished or lost (American Psychiatric Association, 2013), as opposed to “positive” symptoms such as delusions or hallucinations, where a thought or perception function is dysfunctional as increased. Negative symptoms have been considered a core component of schizophrenia since Bleuler’s work (Bleuler, 1911), and they may concern the individual’s personal experience [e.g., decreased expression of emotion

and reactivity to events (*blunted affect*); decreased ability to experience pleasant emotions related to previous, current or future positive events (*anhedonia*), reduced speech output (*alogia*)], or the relation between the individual and the external world [(e.g., lack of interest in social interaction (*asociality*); lack of initiative in goal-directed activity (*avolition*) (Kimhy *et al.*, 2006)].

1.4 Genetics in psychiatry

1.4.1 Brief history of Psychiatric Genetics

Early thoughts on inheritance of psychiatric disorders can be tracked back to the ancient Greeks. For example, Euripides described 'morality' as a hereditary trait; and during the medical revolution of the Renaissance, Paracelsus hypothesised that the disorder affecting the '*insani'* was transmitted from parents to offspring (Schulze *et al.*, 2004). However, the question whether or not mental health conditions were triggered by inherited elements became of research interest only towards the end of the nineteenth century, following the introduction of the theories of Darwin and Mendel, on evolution and inheritance.

Indeed, initial ideas concerning psychiatric inheritance were incorporated in pseudo-sciences such as physiognomy and phrenology, and they were subsequently integrated in Morel's theory of 'degeneration' (Morel, 1860). This was the first conceptualization of psychiatric genetics; hence, as described above, many taxonomists based their classifications of psychotic disorders on a hereditary concept of degeneration. The introduction of a scientific approach in this field is attributed to Sir Francis Galton, who systematically examined complex hereditary

traits such as intelligence (Galton, 1869, 1883), paving the way towards the development of behavioural genetics. At that time, there was a lengthy debate between Galton's 'biometric' scholars headed by Walter Franck Raphael Weldon, who supported the theory of quantitative variations in phenotypes (Weldon, 1902), and the Mendelists headed by William Bateson, who claimed that specific events caused substantial qualitative phenotypic variations across generations (Bateson and Mendel, 1913).

Ernst Rüdin conducted the first systematic family study in psychiatry, reporting a higher lifetime risk of 7.7% for broadly defined schizophrenia in relatives of patients with schizophrenia compared with the general population. However, Rüdin and some other contemporary colleagues were firm supporters of 'eugenics', and their study interpretation was contaminated by racial ideology (Gottesman and Bertelsen, 1996, Schulze *et al.*, 2004).

After World War II, Franz Josef Kallmann completed his controversial study on the existence of a gene predisposing to schizophrenia in US (Kallmann, 1946). However, the UK kept psychiatric genetics alive. Eliot Slater and Valerie Cowie re-considered genetics as a potential link between psychiatry and other medical sciences (Slater and Cowie, 1971); and Slater's pupils, Irving Gottesman and Jerry Shields introduced the concept of polygenicity in schizophrenia (Gottesman and Shields, 1967). These studies were also important as they challenged the contemporary psychoanalytic explanations of schizophrenogenic rearing.

Subsequent evidence from family studies, including twin, sibling, and adoption studies, confirmed the early observations that psychiatric conditions were in part heritable, had a non-Mendelian and polygenic architecture, and could not be entirely explained without considering other factors such as environmental exposure

(Polderman *et al.*, 2015). Specifically, family studies in schizophrenia demonstrated that its heritability was around 80% (Cardno and Gottesman, 2000, Sullivan *et al.*, 2003). The application of genetic epidemiology to major psychiatric disorders gained further interest in the 1990s, when molecular genetic techniques allowed the examination of susceptibility genes in psychiatric disorders. Early molecular studies were based on linkage analyses aiming to identify co-segregation of genetic traits. Although linkage studies would better suit Mendelian diseases than psychiatric complex traits (Bush and Haines, 2010), this approach in the field of schizophrenia proposed some genomic regions of interest (Ng *et al.*, 2009). Subsequently, finer hypothesis-driven approaches were applied to test the association between 'best guess' functional variants within plausible biological pathways and psychiatric expression. These studies led to the identification of several single nucleotide polymorphisms (SNPs) associated with schizophrenia (Farrell *et al.*, 2015). Further studies reported interaction between some of these candidate SNPs and environmental risk factors in conferring synergistic risk towards psychotic disorders (Caspi and Moffitt, 2006). However, most of candidate gene associations and interactions were not consistently replicated (Keller, 2014), and a meta-analysis highlighted their lack of statistical power (Farrell *et al.*, 2015). For example, in the field of depression, Border and colleagues showed no association between any candidate SNPs or G x E interaction with depression phenotypes in a very large population-based and case-control sample (Border *et al.*, 2019). In summary, candidate gene studies were not better than chances for identifying risk variants at least when applied to complex traits, since they carried same limitations as linkage studies. Moreover, meta-analysis results of candidate gene studies should be cautiously interpreted due to the risks of sampling and sampling and publication bias

(e.g. negative results less likely to be published). For example, the largest meta-analysis to date of candidate gene studies in schizophrenia reported 14 Bonferroni-corrected independent loci associated, three of them never reported in Genome Wide Associated Studies (GWAS) (Liu *et al.*, 2019). Nevertheless, candidate gene studies have been highly relevant in the history of psychiatric genetics as they set the grounds for the subsequent GWAS era.

1.4.2 The GWAS era

During the past decade, further advances in molecular biology, reduction in genotyping costs (van Dijk *et al.*, 2014), and strong research collaborations have contributed to a shift towards GWAS, which apply high-throughput methods to examine millions of genetic variants (Lewis and Knight, 2012). Specifically, GWAS are designed to compare the frequencies of common genetic variants (i.e., SNPs with a frequency >1% in the general population) in large samples without having a-priori hypotheses. Availability of large samples has been achieved through consortia such as the Psychiatric Genomic Consortium (PGC); and a high statistical threshold for multiple testing is applied in these studies (p=5x10^{-8}) to minimise the risk of false positives (Sullivan, 2009). The first GWAS in the field of schizophrenia lacked power to identify risk loci. However, the progressive increase in sample size reflected an increasing number of identified loci, moving from one locus identified in 479 cases (O'Donovan *et al.*, 2008) to 108 independent loci in 37,000 cases as part of the second wave of schizophrenia PGC mega-analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), and up to 145 independent loci identified in more than 40,000 cases in the largest published mega-analysis to date (Pardinas *et al.*, 2018, Dennison *et al.*, 2019). More specifically, the relationship

between increase in sample size and number of discovered loci in schizophrenia became linear after having reached an inflection point at about 9,000 cases (Levinson *et al.*, 2014).

The GWAS approach has provided four main contributions so far towards our understanding of psychiatric disorders.

First, it has clarified that the architectural structure of most psychiatric diseases is polygenic, identifying many genetic loci of biological relevance (Collins and Sullivan, 2013, Dennison *et al.*, 2019).

Second, it has demonstrated that the effect size associated with a single common variant is usually minimal, in contrast to what was hypothesised in early candidate gene studies. For example, in current mega-analyses, there is approximately 100% power to find common genetic variants with odds ratio >1.35 (Farrell *et al.*, 2015), which disproves the existence of a single 'gene for schizophrenia'. Rather, psychiatric phenotypes are associated with numerous variants, each having small effect size and conferring a cumulative risk towards developing the condition.

Third, it has showed that there is a partial biological overlap between major psychiatric disorders (e.g., schizophrenia and bipolar disorder) (International Schizophrenia Consortium *et al.*, 2009, Bipolar Disorder Schizophrenia Working Group of the Psychiatric Genomics Consortium and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018). This has expanded the scope of GWAS to cross disorder examinations of domains of psychopathology as well as to seek 'modifier genes' associated with specific clinical features (Fanous *et al.*, 2012, Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.*, 2013, Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019).

Fourth, it has opened the way to the application of new study designs and statistical approaches, such as Polygenic Risk Score (PRS) analyses and precision medicine (Lewis and Knight, 2012, Bogdan *et al.*, 2018).

1.4.3 Polygenic Risk Score analyses

Information from SNPs identified in GWAS studies can be used to explore the extent to which the genetic liability for a specific disorder is expressed in an independent sample (International Schizophrenia Consortium *et al.*, 2009). Using this approach, the risk conferred by several million common genetic variants is summarised in an individual Polygenic Risk Score (PRS). This is computed by summing the number of SNP risk alleles carried, weighted by the effect size from the summary statistics from a large GWAS (International Schizophrenia Consortium *et al.*, 2009).

The application of PRS in the second wave of PGC schizophrenia GWAS, which included 36,989 patients and 113,075 controls, showed that common genetic variants accounted for 18% of the variance in the case-control status (corresponding to 7% of the variation on the liability scale, assuming a lifetime risk of schizophrenia of 1%) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Moreover, the public availability of summary statistic allows PRS for schizophrenia to be constructed in any independent genotyped sample, so researchers can test the extent to which the genetic liability for schizophrenia is correlated with the risk of developing schizophrenia or other phenotypes. For example, PRS for schizophrenia have been associated with a chronic course of the disorder (Meier *et al.*, 2016) and response to treatment (Li *et al.*, 2018). Recently, it has been shown that cognitive deficit in schizophrenia cases was associated with PRS that indexed cognitive traits in the general population rather than PRS for

schizophrenia (Richards *et al.*, 2019). This body of evidence suggests that cognitive variation in schizophrenia depends on the same genetic factors that determine cognition variation in the general population (Mallet *et al.*, 2020).

1.4.4 Translating Polygenic Risk score to everyday clinical practice

PRS can be used to identify individuals who have increased genetic risk for disease. In medical conditions, PRS could be used to identify high-risk subgroups of the population, for early intervention or screening. For example, it has been proposed that mammogram screening programme could start earlier in women with high breast cancer PRS (Mavaddat *et al.*, 2015). The potential value of a PRS clinical approach has been further proposed for coronary disease, where it could identify 8% of the population at a threefold increased risk (Khera *et al.*, 2018). However, currently two main limitations make it difficult to apply this approach in psychiatric clinical practice.

First, PRS does not have a strong predictive value in psychiatry. For example, although schizophrenia PRS is strongly associated with case status, it usually explains less than 10% of the variance in a typical first episode psychosis (FEP) - control study (Vassos *et al.*, 2017), which may increase to 20% in the largest combined chronic samples (Pardinas *et al.*, 2018). This raises the question of missing heritability and suggests that other factors must to be considered for implementing care algorithms in addition to common variants, for example rare variants with higher penetrance and environmental risk factors (Lewis and Vassos, 2017).

Second, largest GWAS samples are mainly composed of individuals of European ethnicity. As a consequence, PRSs have poor predictive value in people of non-

European ancestry, for example of African ancestry (International Schizophrenia Consortium *et al.*, 2009, Vassos *et al.*, 2017). There are concerns that this may increase disparities in the availability of care, thus large GWAS should involve different ethnic groups (Martin *et al.*, 2019). Further, restricting analysis to one population may limit the overall understanding of the genetics of schizophrenia; hence, some authors highlighted the importance of performing trans-ancestral analyses (Dennison *et al.*, 2019). Indeed, some causal variants may differ in allele frequency and linkage disequilibrium (LD) patterns across populations, so that they may be too rare to be identified in one specific population, but they may come out in trans-ancestral examinations.

Hence, schizophrenia GWAS should be expanded beyond European-ancestry populations to cover Asian, African, and Latino populations. Results from a recent East Asian schizophrenia GWAS indicated that the common variant structure of schizophrenia is similar across East Asian and European populations (Lam *et al.*, 2019), with the notable exception of long-range LD regions such as the MHC (Lam *et al.*, 2019). Interestingly, trans-ancestral analyses of Asian and European GWAS identified risk variants that would be too rare in European only samples and filtered out due the low MAF, for example a variant within the *GABBR1* gene, coding for a component of the GABA receptor, discovered in Asian GWAS (Yu *et al.*, 2017).

A recent trans-ancestral analysis of admixed African and Latino schizophrenia GWAS showed that in people of African ancestry, PRS constructed using African GWAS explained more variance than the one constructed using European GWAS; and that European and Latino cases carried more African-derived risk alleles than their ancestry matched controls (Bigdeli *et al.*, 2019).

These findings suggest that generalizability of research findings and application of polygenic risk scoring in clinical practice depend on future availability of risk allele weights from well powered ancestry matched GWAS.

Chapter 2: Genetic and environmental risk factors in non-affective and affective psychosis, and the symptom dimension approach

In the first part of this chapter, I illustrate the similarities and dissimilarities between non-affective and affective psychoses that, as a whole, challenge their conceptualization as discrete entities. Hence, I introduce the neurodevelopmental hypothesis of schizophrenia, which may explain differences in the expression of psychosis. In the second part of this chapter, I describe the extensive body of evidence indicating that cannabis use is a component cause of psychotic disorders, concluding that cannabis-associated psychosis may be integrated into a developmental risk factor model of psychosis. Finally, I explain that individual differences in psychosis may be best examined using a transdiagnostic approach based on symptom dimensions, that may reflect the continuous distribution of biological and environmental risk determinants across the psychosis spectrum.

2.1 Diagnostic validity of non-affective and affective psychotic disorders

The utility of psychiatric diagnostic categories should be distinguished from their validity (Kendell and Jablensky, 2003). From a utility perspective, the introduction of ICD-10 and of DSM-III and their successors led to a worldwide use of a common language, including reporting on psychiatric history, treatments, and outcomes (Kendell and Jablensky, 2003). However, from a validity perspective, research failed to find convergent validators of operationalised ‘disease entities’, at least under the original assumption that psychiatric diagnoses should be mutually exclusive (Stengel, 1959, Zubin, 1961). Robins and Guze, and later Kendler, identified different classes of validators based on their applicability to schizophrenia (Robins and Guze,

1970, Kendler, 1980). For example, Kendler distinguished between antecedent validators (e.g., familial aggregation, premorbid personality, and precipitating factors), concurrent validators (e.g., psychological scales), and predictive validators (e.g., diagnostic consistency, relapse and recovery, and treatment response) (Kendler, 1980). However, dissatisfaction with the distinction between schizophrenia, schizoaffective, and affective psychoses was evident due to the failure to discriminate these entities based on psychiatric history, mental state and even follow-up data (Brockington *et al.*, 1979). Moreover, epidemiological data clearly emphasised these difficulties. For example, the Camberwell Register study showed that at FEP, two out of three patients had a diagnosis of schizophrenia according to RDC criteria, but only one out of three patients had the same diagnosis when using DSM-III or Feighner criteria (Castle *et al.*, 1991). In addition, it became clear that classifying patients presenting both prominent mood and psychotic symptoms into the category of schizoaffective disorders had created further nosological challenges (Abrams *et al.*, 2008). For example, a recent meta-analysis of 49 studies showed that the mean test-retest reliability of schizoaffective disorder (κ=0.57) was lower compared with schizophrenia (κ=0.69), bipolar disorder (κ=0.77) and unipolar depression (κ=0.73) (Santelmann *et al.*, 2016).

2.1.1 Validity of alternative categorical subtyping

Hence, in the 1980s there were several efforts to operate a clear-cut division of schizophrenia into discrete sub-categories. That is, subtypes accounting for the predominance of positive or negative symptoms were proposed to identify positive, negative and mixed schizophrenia (Andreasen and Olsen, 1982); subtypes accounting for family history were proposed to differentiate familial from sporadic schizophrenia

(Murray *et al.*, 1985); and subtypes based on primary enduring or transient negative symptoms were proposed to differentiate a 'deficit syndrome' from a non-deficit schizophrenia (Carpenter *et al.*, 1988). Tim Crow split schizophrenia into two-syndromes, of which type I would have been similar to Bleuler's schizophrenia and type II to Pinel-Haslam's schizophrenia (postulating a neurodegenerative process) (Crow, 1985). Later, Murray and colleagues proposed to discriminate neurodevelopmental forms from adult-onset schizophrenia (Murray *et al.*, 1992), and indeed this was well supported by latent class analyses. However, this subclassification maintained the difficulty on how to interpret the intermediate schizoaffective subtype (Castle *et al.*, 1994, Sham *et al.*, 1996).

Overall, there is evidence supporting the utility of sub-classifications (Fenton and McGlashan, 1994), especially when comparing the two extremes of opposed subtypes. However, all sub-categories carry the same methodological limitation as traditional diagnostic categories, i.e. poor validity of these constructs and the necessity to introduce intermediate phenotypes.

2.1.2 Recent epidemiological studies on affective and non-affective psychosis

The Kraepelinian paradigm has been consistently challenged by the large comorbidity indices between schizophrenia, schizoaffective, bipolar, and major depressive disorders (Laursen *et al.*, 2009, Upthegrove *et al.*, 2017). In addition, mounting evidence has been suggesting that the incidence of psychotic disorder is extremely heterogenous in time and place (McGrath *et al.*, 2004). In South London, the examination of the Camberwell register showed that the incidence of psychosis has been increasing over a 30 year time (Boydell *et al.*, 2003). Findings from the

Aetiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) incidence and outcome studies of psychosis suggests that the increase may be in part due to the massive migration phenomenon (Fearon *et al.*, 2006). The ÆSOP study also showed that incidence varied across place, being higher in Southeast London than in Nottingham and Bristol (Kirkbride *et al.*, 2006). In addition, the ten-year outcomes of the study (ÆSOP-10) suggested that diagnoses within psychosis spectrum other than schizophrenia at baseline tended to be unstable over time (Heslin *et al.*, 2015). Further evidence that the incidence of psychosis is unstable comes from a recent comprehensive systematic review and meta-analysis, indicating a pooled incidence of all psychotic disorders of 26.6 per 100 000 person-years. The pooled incidence was 18.7 per 100 000 person-years for non-affective psychotic disorder and 4.6 per 100 000 person-years for affective psychotic disorders, however there was a large geographical variation in part explained by differences in case ascertainment methods (Jongsma *et al.*, 2019). The 'European Network of National Schizophrenia Networks studying Gene-Environment Interactions' (EU-GEI) study addressed this bias by examining the incidence of psychotic disorders using same ascertainment methodology and standardised research-based diagnoses from the Operational Criteria checklist (OPCRIT) across six different countries. The study showed a marked heterogeneity in the risk of developing a psychotic disorder, by person and place, with an global incidence rate of psychotic disorders of 21.4 per 100,000 per year (non-affective psychosis: 16.9 per 100 000 person-years; affective psychosis: 4.3 per 100 000 person-years) with an eight fold variation of the incidence rates across the study sites (Jongsma *et al.*, 2018).

It is plausible that socioenvironmental and biological factors account for such a large variation in the incidence of psychosis. Di Forti and colleagues examined this

hypothesis, showing that daily cannabis use and use of high potency cannabis were two important contributors accounting for variation in the incidence rates of psychosis across the EU-GEI study sites, even accounting for age, gender, and ethnic minority status (Di Forti *et al.*, 2019a).

In summary, epidemiological research into psychotic disorders has clearly challenged the old idea of the existence of discrete natural disease entities with a homogenous and unchanging distribution.

Further epidemiological evidence challenging a categorical definition of psychosis concerns the continuous distribution of delusions and hallucinations, as well as of negative psychotic experiences, in the general population (van Os *et al.*, 2009). Data indicate that there are no discrete breaks in the distribution of symptoms, hence the threshold between subclinical and clinical psychosis would be dictated by social or contextual norms, reflecting qualitative or quantitative differences in symptomatology. For example, the presence of hallucinations extends trans-diagnostically beyond schizophrenia to other psychotic and non-psychotic disorders (de Leede-Smith and Barkus, 2013) and to the general population (Linscott and van Os, 2013). Despite methodological differences among studies, a median prevalence of hallucinations of 13.2% was reported in the adult population (Beavan *et al.*, 2011). In a recent quantitative review and meta-analysis, Maijer et al. (2018) aimed to calculate an accurate mean lifetime prevalence of auditory hallucinations in the general population, reporting a pooled estimated prevalence of 9.6% across 25 studies (Maijer *et al.*, 2018). Hence, hallucinations may be regarded as a continuous, or extended, phenotype ranging from symptoms of a clinical disorder to a transient phenomenon in the general population. Similarly, a proportion of 10% to 15% of the general population regularly experience delusional ideas of various degrees,

reaching in 1 to 3% of individuals a severity comparable to clinical cases of psychosis (Freeman, 2006).

2.1.3 Pharmacology and clinical practice in affective and non-affective psychosis

Two different pharmacology trajectories between schizophrenia and bipolar disorder (e.g., involving the use of lithium and other mood stabilisers) have been traditionally considered as a key element supporting a neat distinction between schizophrenia and bipolar disorder. However, several studies showed the efficacy of agents which impact on dopamine signalling in treatment of both non-affective and affective symptoms. For example, antipsychotics antagonise D2 dopamine receptor functioning and are used in bipolar disorder and schizophrenia (Post, 1999, Taylor *et al.*, 2015), and clozapine is indicated for both treatment resistant schizophrenia and treatment resistant mania (Li *et al.*, 2015, Howes *et al.*, 2016, Fountoulakis *et al.*, 2019). These findings suggest that dopamine dysregulation may contribute to both positive and manic symptoms, as supported by positron emission tomographic findings (Jauhar *et al.*, 2017). Moreover, mood stabilisers are used as add-on treatment in schizophrenia as they may contribute to reduce the severity of positive symptomatology (Casey *et al.*, 2009). Altogether, these findings are in line with the original Brockington's consideration that lithium and chlorpromazine would be equally effective in the treatment of the intermediate group composed of schizoaffective patients (Brockington *et al.*, 1978).

2.2 An alternative developmental perspective in psychotic disorders

2.2.1 Pre- and peri-natal factors in non-affective and affective psychosis

The post-modern conceptualization of schizophrenia as a neurodevelopmental disorder (Murray and Lewis, 1987, Weinberger, 1987) has emerged in the 1980s from studies showing that monozygotic twins with schizophrenia had larger cerebral ventricles than their healthy counterpart, particularly if they were exposed to perinatal hazards (Reveley *et al.*, 1982, Reveley *et al.*, 1984). Subsequent studies have confirmed that obstetric complications, e.g. pregnancy complications, fetal growth/development abnormalities, and delivery complications, were risk factor for schizophrenia (Lewis and Murray, 1987, Cannon *et al.*, 2002b); however, no robust evidence has indicated an association between these complications and bipolar disorder (Scott *et al.*, 2006). Moreover, perinatal hypoxia or asphyxia has been consistently associated with reduced volume of the amygdala and hippocampus (Murray *et al.*, 2004), which is a brain structural pattern more common in schizophrenia than bipolar disorder (see paragraph 2.2.4). Similarly, fetal growth indicators such as low birth weight or small birth length well correlated with schizophrenia but not with bipolar disorder (Ogendahl *et al.*, 2006). Moreover, maternal viral infections, especially influenza, have been associated with schizophrenia (Brown, 2006, Boksa, 2008, Benros *et al.*, 2011, Kępińska *et al.*, 2020). On the other hand, evidence on the association between these infections and bipolar disorder is less consistent (Marangoni *et al.*, 2016, Kępińska *et al.*, 2020).

2.2.1 Early neurodevelopmental impairment in non-affective and affective psychosis

In 2000s, the Dunedin study showed that an impairment in cognitive and neuromotor development during childhood was associated with developing schizophrenia but not bipolar disorder later in life (Cannon *et al.*, 2002a). Indeed, cognitive deficit is a well-established component of schizophrenia and it has been integrated into the developmental risk model of schizophrenia (Howes and Murray, 2014). However, it has been debated whether cognitive deficit follows a neurodevelopmental or neurodegenerative pattern. There is evidence that cognitive dysfunction is already present before the onset of psychosis (Bora and Pantelis, 2015), and even before the prodromal stage (Bora and Murray, 2014); however, it is difficult to ascertain the natural course of such a dysfunction after psychosis onset, given the confounding effect of several factors, for example the use of antipsychotics and hospitalizations. Longitudinal studies have found no clear evidence of cognitive decline, and it has been showed that such a decline would be restricted to some cognitive domain such as verbal knowledge and memory, whereas executive functions would remain stable over time (Zanelli *et al.*, 2019). Noteworthy, cognitive deficit appears to be less common and less severe in bipolar disorder, and this difference may index two different neurodevelopment trajectories towards developing schizophrenia and bipolar disorder (Trotta *et al.*, 2015). Consistent with these findings, a relationship has been found between cognitive deficit and negative symptoms (Kravariti *et al.*, 2012), which are often considered being a marker suggestive of early neurodevelopment impairment in schizophrenia. Of note, a large register-based cohort study showed that children achieving excellent performance were more at risk of developing bipolar disorder than schizophrenia (MacCabe *et al.*, 2010).

2.2.3 Brain structure in non-affective and affective psychosis

Neuroimaging studies have shown that schizophrenia and bipolar disorder carry different brain structural abnormalities. From this perspective, findings from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium, integrating data from 70 different institutions, are particularly relevant. Specifically, the ENIGMA study indicated that patients suffering schizophrenia have a thinner cortex and smaller surface area, especially in frontal and temporal lobe regions (van Erp *et al.*, 2018); whereas patients suffering bipolar disorder have a thinner cortical grey matter in frontal, temporal and parietal lobe regions (Hibar *et al.*, 2018); moreover, antipsychotics and mood stabilisers may be both associated with cortical thickness. In the largest examination of first-degree relatives of patients with schizophrenia or bipolar disorder, the ENIGMA study also concluded that family aggregation of brain abnormalities is disease specific. That is, in comparison with healthy individuals, relatives of patients suffering bipolar disorder patients had a larger intracranial volume, whereas relatives of patients suffering schizophrenia had smaller cortical grey matter, cerebellar grey and white matters, cerebral white matter, and thalamus, with a thinner cortex and enlarged lateral and third ventricles (de Zwarte *et al.*, 2019). Given that intracranial volume is considered a proxy of early brain development, the authors suggested that two different neurodevelopment trajectories may underpin brain structural differences between schizophrenia and bipolar disorder (de Zwarte *et al.*, 2019).

Interestingly, the ENIGMA study further showed that common genetic variation may account to some extent for variation in subcortical volumes (Satizabal *et al.*, 2019),

involving SNPs within genes operating in brain development and neuronal signalling, and in part overlapping with schizophrenia or autism spectrum disorders.

2.2.3 Genetic studies in non-affective and affective psychosis

From a genetic perspective, the Kraepelin's paradigm is not consistent with the accumulated evidence that genetic risk is in part shared by schizophrenia and bipolar disorder (International Schizophrenia Consortium *et al.*, 2009, Demjaha *et al.*, 2011, Cardno and Owen, 2014, O'Donovan and Owen, 2016, Power *et al.*, 2017). Family studies showed familial co-aggregation of non-affective and affective psychosis (Cardno *et al.*, 2002, Lichtenstein *et al.*, 2009, Chou *et al.*, 2017). Moreover, similar concordance rates were found for schizophrenia, schizoaffective, and mania in both monozygotic (47-57%) and dizygotic (14%) twins (Cardno *et al.*, 1999). Interestingly, GWAS identified SNPs associated with both bipolar disorder and schizophrenia in *CACNA1C, ANK3, ITIH3-ITIH4, ZNF804A* and *NCAN* but also SNPs (e.g., in *MHC, ODZ4, TCF4*) specific for either disorder separately (Hamshere *et al.*, 2013, Bipolar Disorder Schizophrenia Working Group of the Psychiatric Genomics Consortium and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018, Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). The latest cross-disorder PGC metanalysis showed that schizophrenia and bipolar disorder had a SNP-based genetic correlation of 0.7, and several SNPs (N=109) had a pleiotropic effect across different psychiatric disorders, of which 83% and 72% involved schizophrenia and bipolar disorder respectively (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Moreover, the latest Psychiatric Genomic Consortium Bipolar and Schizophrenia Working Groups GWAS showed that four genomic regions contributed to differences between

schizophrenia and bipolar disorder, including disorder-independent causal variants and potassium ion channel genes (Bipolar Disorder Schizophrenia Working Group of the Psychiatric Genomics Consortium and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018). Furthermore, in this study schizophrenia PRS was associated with psychotic features in bipolar disorder (Bipolar Disorder Schizophrenia Working Group of the Psychiatric Genomics Consortium and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018).
On the other hand, genetic elements consistently supporting dissimilarities between diagnostic categories of psychosis involve the contribution of rare variants (minor allele frequency <1%). For example, an enrichment of large copy number variants (CNVs) was reported in schizophrenia (Gulsuner and McClellan, 2015, Marshall *et al.*, 2017), while whether CNVs contribute to bipolar disorder is not clear (Green *et al.*, 2016). More specifically, an enrichment in pathways associated with the postsynaptic density has been reported in schizophrenia but not in bipolar disorder (Fromer *et al.*, 2014, Kataoka *et al.*, 2016). However, consistent with the difficulties in operating a neat Kraepelin's distinction, it has been shown that CNVs exert their contribution in those patients with a diagnosis of 'schizoaffective disorder bipolar type' but not of bipolar disorder (Charney *et al.*, 2019). Moreover, investigations of neurodevelopmental conditions have revealed that recurrent structural variants in schizophrenia, such as 1q21.1, 15q11.2, 15q13.3, 16p13.3, and 22q11.2, have a raised frequency in more than one conditions, including developmental delay, intellectual disabilities, autism spectrum disorders, and multiple congenital abnormalities (Grozeva *et al.*, 2012, Rosenfeld *et al.*, 2013, Watson *et al.*, 2014). Further support to the hypothesis that 'neurosusceptibilty' variants confer susceptibility to a range of neurodevelopment conditions, is provided by a recent UK

Biobank study, showing that CNVs involved in neurodevelopmental disorders are associated with a subtle cognitive deficit even in unaffected individuals with a disadvantage in educational attainment (Kendall *et al.*, 2019).

2.2.4 Non-affective and affective psychosis according to a neurodevelopment model

In summary, altogether the above evidence is consistent with the conclusions of Murray and colleagues (2004) that: '*A plausible model to explain both the overlap and the distinctions between schizophrenia and bipolar disorder needs to invoke both common and unique risk factors: certain susceptibility genes, shared between schizophrenia and bipolar illness, can be thought of as predisposing individuals to psychosis in general. However, other genes (for example, genes involved in neurodevelopment) and/or environmental factors (pre- and perinatal complications, winter/spring birth, city birth) may then act, or interact, upon this background to launch an individual on a trajectory towards schizophrenia.*' (Murray *et al.*, 2004).

2.3 Cannabis use and psychosis

2.3.1 Case series on cannabis and psychopathology

There has been a long history of interest in the association between cannabis and psychopathology. Early concerns on cannabis use were focused on the risks of committing crimes whilst intoxicated. For example, Peebles reviewed admission data at the Agra Lunatyc Asylum in India over ten years, concluding that 25% of the admitted patients had used cannabis; and 25% of those who were in the Asylum as

a consequence of having committed a crime (including serious crimes such as murder, arson, or felonious assault) had done it due to the use of cannabis (Peebles, 1914). The association between cannabis use and psychosis has also been extensively reported in the form of case series. For simplicity, I summarise here five reports (Bromberg, 1934, Talbott and Teague, 1969, Spencer, 1971, Bernhardson and Gunne, 1972, Chopra and Smith, 1974), although the evident value of several similar reports is weakened by the study design limitations.

In the case series of marijuana intoxication described by Bromberg (1934) in the USA, different psychopathology outcomes are described, including (1) the acute intoxication, (2) a mania, *'which is an acute intoxication with manic-like features*, (3) the toxic psychoses with delusional and hallucinatory experiences, (4) the toxic admixture of cannabis to other psychoses and (5) a so-called "dementia" (an end-state of years of cannabis usage with ethical, intellectual and volitional deterioration). Fifty per cent of the cases with intoxication had a symptom pattern characterised by delusions and 36% by auditory hallucinations. These particular cases were described as having '*toxic psychoses'* that '*are long-lasting and may go on to an atypical manic or depressive or schizophrenic psychosis'*.

Later, Spencer (1971) reported that people with cannabis associated psychosis were very florid in their positive symptomatology. Talbott and Teague (1969) observed, in Vietnam, acute psychosis following cannabis use in soldiers, with delusions or hallucinations being a general part of the presentation in 10 out of 12 cases. Interestingly, at that time, Vietnamese marijuana was as twice as potent as American marijuana, which may have contributed to a more severe symptom profile observed in Vietnam. Consistent with Talbott and Teague, Gunne (1972) described a symptomatology characterised by auditory hallucinations in about half of 46 habitual

users of cannabis in Sweden; and Chopra and Smith (1974) reported the worst symptomatology (which included mostly visual hallucinations) in the group of people using *ganja* or *charas*, the two most potent varieties of cannabis available at the time in India.

2.3.2 Epidemiological studies: cannabis use as a 'causal' factor for psychosis

'Causality' implies that exposure to a noxa is a necessary, sufficient or contributory cause to develop a certain condition (Rothman and Greenland, 2005). Epidemiological methods for making causal inferences include ascertaining the strength of the association, its temporal direction, and the existence of a dose-response effect (Rothman and Greenland, 2005), although broader criteria may apply when findings across different studies are convergent (Hill, 1965).

Strength of the association

The first systematic study which prospectively suggested an association between cannabis and psychosis was carried out in Sweden among conscripts, showing that those who had used cannabis more than fifty times in their life were six times more at risk to develop schizophrenia than those who had not used cannabis (Andreasson *et al.*, 1987).

The Dunedin study further clarified that the risk was higher if starting to use cannabis during adolescence (Arseneault *et al.*, 2002); and in the NEMESIS longitudinal study, van Os and colleagues went to show that use of cannabis was associated with subclinical psychotic symptoms in the general population (van Os *et al.*, 2002a). Subsequently, a large body of epidemiological evidence demonstrated an

association between the cumulative exposure to cannabis and non-affective psychotic outcomes (Di Forti and Murray, 2005, Moore *et al.*, 2007, Murray *et al.*, 2007, Murray and Di Forti, 2016). Moreover, experiencing psychotic symptoms has been reported in over half of a sample of polysubstance abusers who used cannabis, either while using or withdrawing cannabis (Smith *et al.*, 2009).

Di Forti and colleagues (2015) took further into account the potency of cannabis, identifying as high-potency the varieties, in London, containing high concentration of Delta-9 Tetrahydrocannabinol (Δ9-THC) and low concentration of cannabidiol (CBD), such as *'skunk'* (Di Forti *et al.*, 2015). Indeed, in the Genetic And Psychosis (GAP) study, they showed that the highest risk of developing a psychotic disorder was carried by subjects using skunk on a daily basis (Di Forti *et al.*, 2015).
Moreover, many studies showed that the association between exposure to cannabis and later onset of psychosis held after controlling for any currently known socio-environmental factor associated with psychotic disorders. For example, in the EU-GEI study, daily use of high potency cannabis increased the risk of psychotic disorder of 5 fold compared to never use independently of co-exposure to eight different types of other drugs (including tobacco), IQ, level of education, employment and relationship status, gender, age, urban or rural context, and ethnic group (Di Forti *et al.*, 2019a).

Evidence that cannabis use increases the risk of bipolar disorder is less consistent (Moore *et al.*, 2007). Of note, a systematic review of three prospective studies showed that individuals who used cannabis weekly would have an increase in the risk ranging from 2.5 to 9 times to develop bipolar disorder than those not using cannabis (Marangoni *et al.*, 2016, Sideli *et al.*, 2019).

Chronological causality

It is widely recognised that prospective population-based studies are gold-standard for establishing chronological relationship between exposure to a factor and subsequent outcome. These studies have consistently shown that use of cannabis precedes the development of schizophrenia. For example, in the previously mentioned Dunedin birth cohort study, 96% of 1,037 new-born individuals were followed up until the age of 26 (Arseneault *et al.*, 2002). Findings showed the existence of a relationship between the use of cannabis at age 15 and a diagnosis of schizophrenia at the age of 26 (Arseneault *et al.*, 2002). Moreover, convergent findings were reported in other high-quality population-based studies, including the previously mentioned pioneer study on conscripts in Sweden (Andreasson *et al.*, 1987) and the NEMESIS study in Holland (van Os *et al.*, 2002a).

Dose-response effect

Finally, there is consistent evidence that cannabis exposure and onset of psychosis follows a dose-response relation risk. A metanalysis confirmed that individuals with heavy cannabis use had an odds ratio (OR) of 3.90 (95% CI 2.84 to 5.34) for the risk of schizophrenia and other psychosis-related outcomes compared to nonusers, which indicates a moderate to large effect (Marconi *et al.*, 2016).
Furthermore, potent cannabis varieties have become available worldwide (Freeman *et al.*, 2019) and importantly, as presented above, increasing availability of high potency cannabis may impact on the incidence rates of psychotic disorders across Europe (Di Forti *et al.*, 2019a), to the point that not only the frequency of use but also

the potency of cannabis are now recognised as vital information for conducting high-quality research into this field (Di Forti *et al.*, 2019a, Freeman and Lorenzetti, 2019).

Conclusions based on the above evidence

1) Is cannabis use a sufficient cause of the disorder?

Longitudinal cohort studies show that only a minor proportion of the adolescents who use cannabis develop a psychotic disorder later in life, hence the conclusion is that cannabis is not a sufficient cause of schizophrenia.

2) Is cannabis use a necessary cause of the disorder?

Individuals may develop schizophrenia without having had any lifetime exposure to cannabis, hence, the conclusion is that cannabis use is not a necessary cause of schizophrenia. However, I also argue that this is not entirely falsifiable due to the use of current diagnostic system. Indeed, as widely discussed in this thesis, diagnostic categories are useful constructs for clinical practice, but they are arbitrary as nosological constructs. In a hypothetical scenario where Bonhoeffer was more influential than Kraepelin and an exogenous cannabis-associated psychosis would exist as an official diagnosis, cannabis use would be a necessary (though not sufficient) cause of that disorder.

3) Is cannabis use a contributory cause of the disorder?

Altogether, the above evidence clearly demonstrate that cannabis use is a contributory cause of the disorder. This conclusion is consistent with what is currently known about complex multifactorial disorders, where both genes and socio-

environmental factors are neither sufficient nor necessary causes to the disorder, but they interact with each other to confer risk.

2.3.3 Experimental studies on cannabis and psychotic symptoms

Experimental studies have shown that Δ9-THC administration results in short-lived psychotic symptoms (Morrison *et al.*, 2009, Winton-Brown *et al.*, 2011) and brief negative symptoms (Morrison and Stone, 2011) in healthy volunteers, and in a worsening of psychotic symptoms in individuals with schizophrenia (D'Souza *et al.*, 2005). On the other hand, psychoactive effects of Δ9-THC could be contained by the co-administration of CBD (Englund *et al.*, 2013). However, a recent meta-analysis of 15 studies confirmed that acute administration of Δ9-THC in healthy volunteers induces positive symptoms with large effect size to a greater extent than negative symptoms, whereas the evidence for the counterbalancing effect of CBD on these symptoms remains inconclusive (Hindley *et al.*, 2020). In addition, the use of synthetic cannabinoid receptor agonists, commonly known as ‘spice’, has increased over recent years. These substances are more potent than the Δ9-THC contained in traditional cannabis (van Amsterdam *et al.*, 2015), and their use can induce florid psychotic symptoms and hallucinations (Papanti *et al.*, 2013).

2.3.4 Biological plausibility of the association between cannabis use and experiencing psychotic symptoms

Δ9-THC elicits its acute psychoactive effects firstly interacting with the endocannabinoid system, a lipid signalling neuromodulatory pathway (Piomelli *et al.*, 2000, Piomelli, 2003, Fakhoury, 2017) which plays a primary role in synapse

formation and neurogenesis (Harkany *et al.*, 2008), and in modulating synaptic strength mostly through retrograde signalling (Kano *et al.*, 2009) especially during adolescence (Viveros *et al.*, 2012, Meyer *et al.*, 2018). The endocannabinoid system includes (1) at least two endocannabinoid receptors (CB1R and CB2R), (2) the endocannabinoid ligands, such as anandamide and 2-arachidonoylglycerol, and (3) their synthetic and degradative enzymes. Δ9-THC is an exogenous partial agonist of the CB1R (Pertwee, 2008), which is located pre-synaptically on GABAergic and glutamatergic neurons inhibiting neurotransmitter release. The distribution of CB1 receptor is most abundant in key areas involved in psychosis, for example pre-frontal cortex, basal ganglia, and hippocampus (Mackie, 2005). THC psychotropic effect can be perhaps attenuated by CBD, which may act as an antagonist for CB1R even though it is said to lack affinity for this receptor (Thomas *et al.*, 2004, Thomas *et al.*, 2007). Synthetic cannabinoid receptor agonists, like 'spice', mimic the action of Δ9-THC, but they are full agonists of CB1R, for which they have high affinity. Thus, consumption of synthetic cannabinoids results in stronger effects compared with the Δ9-THC derived from the plant cannabis, and there are reports showing severe perceptual disturbances including hallucinations in people using spice (Hurst *et al.*, 2011, Lerner A *et al.*, 2014, Besli *et al.*, 2015).

Some suggest that Δ9-THC's effects are mediated by the dopaminergic system (Murray *et al.*, 2014, Bloomfield *et al.*, 2016). Disruption in dopaminergic system is thought to be the final mechanism underpinning psychotic disorders, and especially positive symptoms (Di Forti *et al.*, 2007, Howes and Murray, 2014). Certainly, as previously mentioned, the endocannabinoid system modulates dopaminergic neurons through retrograde signalling. Animal research suggests that endogenous cannabinoids, anandamide and 2-arachidonoylglycerol stimulate dopamine release

in the nucleus accumbens after binding CB1R (Oleson and Cheer, 2012); and exogenous cannabinoids, such as Δ9-THC, enhance dopaminergic cell firing as well as dopamine synthesis and release in different brain regions (Bloomfield *et al.*, 2016). However, the interaction between endocannabinoids and dopamine system is complex and requires more research. Studies of the effects of Δ9-THC on striatal dopamine in humans have been inconsistent.

Studies on candidate genes involved in the dopamine system have raised the question of gene x cannabis exposure interaction in psychotic outcomes, in both people with psychosis and population controls (Murray *et al.*, 2016). Specifically, the most reported SNPs in interaction with cannabis are rs4680 in COMT; rs2494732 in AKT1; and rs1076560 in DRD2.

First, the COMT polymorphism Val158Met was tested for interaction with the use of cannabis during adolescence. The authors reported increased risk of hallucinatory experiences in adulthood among Val/Val individuals (OR = 5.3, 95% CI: 2.2–12.7) and, to a lesser extent, among Val/Met individuals (OR = 2.6, 95% CI: 1.4–4.9), but not among Met/Met individuals (OR = 1.2, 95% CI: .50–3.0) for those exposed to cannabis compared with the not-exposed counterpart (Caspi *et al.*, 2005). This is the only interaction that has been studied enough to allow a small meta-analysis, which showed that the initial findings were not confirmed (Vaessen *et al.*, 2018). Three studies which used continuous outcomes found no interaction between this COMT polymorphism and cannabis use on the severity of positive symptoms (Vaessen *et al.*, 2018), which is consistent with an experimental study reporting no effect on THC-induced psychotic symptoms (Tunbridge *et al.*, 2015).

Second, two studies suggested that the AKT1 polymorphism increases risk of psychotic illness among cannabis users (van Winkel *et al.*, 2011, Di Forti *et al.*, 2012). In addition, van Winkel (2011) showed that this interaction was associated with scoring higher at positive schizotypy (van Winkel *et al.*, 2011). Consistently with these findings, another study has shown that this polymorphism is associated with a more severe psychotogenic response to cannabis (Morgan *et al.*, 2016).

Third, it has been reported that the DRD2 polymorphism increases psychosis risk in people using cannabis more than in those not using cannabis (Colizzi *et al.*, 2015b). It has been finally reported that cannabis users carrying the risk variants in both DRD2 and AKT1 genes are at an even higher risk of developing psychosis (Colizzi *et al.*, 2015a).

All of the above reports concerning candidate genes should be treated with caution pending further replication. Current research is focusing on whether the genetic liability to schizophrenia, summarised by PRS may modify the association between cannabis use and psychosis. Indeed, Di Forti and colleagues reported that both schizophrenia PRS and cannabis use, independently from each other, increase the risk of experiencing a FEP (Di Forti *et al.*, 2019b).

2.3.5 Cannabis-associated psychosis and neurodevelopmental trajectories

It is crucial to ascertain if the psychopathology profile of cannabis-associated psychosis is different from schizophrenia and other psychotic disorders in people not using cannabis. Certainly, psychotic symptoms elicited by cannabis improve rapidly

in most people, however it is noteworthy, the continued use of cannabis can shape a clinical picture which is in the long run undistinguishable from schizophrenia-like psychosis (Manrique-Garcia *et al.*, 2012). Schoeler et al. (2016) suggested that cannabis-associated psychosis is characterised by worse outcome when the use of cannabis is protracted over the course of the disorder; specifically, they reported, in the GAP sample, that patients who continued to use cannabis on a daily basis after FEP were at a higher risk of a subsequent psychosis relapse (OR 3.28; 95% CI 1.22–9.18) and involved in more intense psychiatric care (OR 3.16; 95% CI 1.26–8.09) (Schoeler *et al.*, 2016b). These results are in line with a comprehensive review of literature and meta-analysis (Schoeler *et al.*, 2016a).

The developmental risk factor model of psychosis has expanded to account for environmental factors, including adverse life events and social contexts, and use of drugs such as cannabis (Murray *et al.*, 2017a). Neurodevelopmental aberrancies may occur during different pre/peri-natal, childhood or adolescence stages. Regardless of diagnostic categories of non-affective or affective psychotic disorders, cannabis-associated psychosis may not involve early neurodevelopment impairment but disruptions occurring in adolescence, when cannabis is mostly used. For example, compared with those not using cannabis, patients with psychosis who use cannabis have higher IQ and premorbid IQ (Ferraro *et al.*, 2013, Loberg *et al.*, 2014), better premorbid social functioning (Ferraro *et al.*, 2019), and less neurological soft signs (Ruiz-Veguilla *et al.*, 2012).

2.4 The transdiagnostic approach based on symptom dimensions in psychoses

As previously described, according to the developmental risk model of psychosis, children carrying early abnormalities in neural networks (due to genetics and/or medical events) may experience a deficit in neuro- and social cognition and take on a trajectory of scholastic and social difficulties, resulting often in social isolation and deficits in emotional expression (Murray *et al.*, 2017a). These difficulties, which may unfortunately attract further risk events for psychosis such as bullying, often result in prominent primary negative symptoms at first episode of psychosis (FEP) (Murray *et al.*, 2017a). Other socioenvironmental risk factors, including cannabis use, may elicit neurodevelopmental aberrancies later in adolescence, contributing to a phenotype that would be than characterised by less negative symptoms (Murray *et al.*, 2017b). However, current diagnostic categories may obscure the actual distribution of psychotic symptoms (Dikeos *et al.*, 2006), whereas a transdiagnostic approach based on symptom dimensions may be more appropriate to evaluate the extent of developmental risk across the psychosis spectrum [i.e. the 'neurodevelopmental continuum' (Owen and O'Donovan, 2017)]. The symptom dimension approach is based on the assumption that psychotic symptoms follow a continuous distribution (van Os and Tamminga, 2007, Tesli *et al.*, 2014), and on the possibility to statistically identify groups of symptoms that occur together more often than by chance alone, which may also coexist in the same individual (Allardyce *et al.*, 2007a, Demjaha *et al.*, 2009, Russo *et al.*, 2014a).

In social science, this approach is used for measuring constructs that cannot be directly measured due to their latent structure. In recent years, studying psychosis using symptom dimensions has become popular, due to the crisis of confidence in

traditional nosology (Jablensky, 2005, Zachar and Kendler, 2017). However, it may be surprising that the symptom dimension approach is not novel in psychosis. In 1933, a first relevant factor analysis on psychotic symptoms was computed by hand by Thomas Moore on 367 patients from two mental health institutions, in Baltimore and Anacostia (Moore, 1933). Moore identified symptom dimensions of 1) cognitive defect 2) catatonic syndrome; 3) uninhibited or kinetic syndrome; 4) non-euphoric manic syndrome; 5) euphoric manic syndrome; 6) delusional hallucinatory syndrome; 7) syndrome of constitutional hereditary depression; and 8) syndrome of retarded depression (Moore, 1933). One year later, Thurstone, an expert in factor analysis, re-analysed Moore's data, identifying a latent structure composed of five groups of symptoms, i.e. 1) catatonic, cognitive, manic, hallucinatory (which included both delusions and hallucinations), and depressive symptoms (Thurstone, 1934). In 1952, these data were re-analysed once again by Degan, who conveyed on a nine-factor solution, with higher-order domains that were interpreted as mania, hebephrenic schizophrenia, depression, and catatonic schizophrenia (Degan, 1952). More recently, Blashfield identified a five-factor structure in line with Thurstone's work (Blashfield, 1984).

Interestingly, even if different factor analysis identified a very similar latent structure, symptom dimensions were differently interpreted. For example, Degan proposed that the syndromes identified through his work reflected different psychological defence mechanisms, which was consistent with the psychoanalytic approach common in America after World War II (Fenichel, 1945). Indeed, it could be observed that 'Factor A' of Degan's analysis was mainly composed of items indicating paranoid delusions, hallucinations and lack of insight, which would currently correspond to a

positive symptom dimension, but it was interpreted at the time as a ‘hyper-projection’ syndrome.

After operationalization, the first studies investigating symptom dimensions in schizophrenia produced different models, initially including three schizophrenia factors (Liddle, 1987), such as reality distortion, psychomotor poverty, and disorganization. Overall, this factor analysis added the disorganization dimension to the classic Andreasen’s subtyping of positive and negative schizophrenia. This structure was widely replicated, and a meta-analysis of ten studies confirmed the three-factors structure (Grube *et al.*, 1998). On the other hand, other studies privileged a structure with four or five schizophrenia factors (Lindenmayer *et al.*, 1994, Peralta *et al.*, 1994, Wickham *et al.*, 2001).
Nevertheless, it was observed that these factors could not accommodate the whole symptom diversity in schizophrenia (Kay and Sevy, 1990). Thus, psychopathology models including also depressive and manic factors were proposed and replicated in schizophrenia (Lindenmayer *et al.*, 1994, Salokangas, 1997, Wickham *et al.*, 2001, Wallwork *et al.*, 2012). However, the use of schizophrenia samples was a limitation because, as McGorry has pointed out, the heterogeneity of psychosis would have been better studied at FEP (McGorry *et al.*, 1998). Further, this approach allowed to set a common time point for all the patients. Hence the five-factor structure was confirmed in psychotic disorders (Salokangas, 2003, Dikeos *et al.*, 2006, Demjaha *et al.*, 2009), and in first-episode psychosis sample (McGorry *et al.*, 1998). Finally, it was confirmed in a sample of bipolar patients only (Lindenmayer *et al.*, 2008). Hence, its validity across the spectrum of non-affective and affective psychosis has been consistently supported.

Collectively, such evidence has demonstrated the validity of the dimensional representation of psychosis, and that schizophrenia factors extend beyond schizophrenia, encompassing all forms of psychosis independently from the diagnosis. Moreover, it has been shown that such symptom dimensions explain more clinical characteristics than diagnostic categories alone (Dikeos *et al.*, 2006, Russo *et al.*, 2014b), thus allowing us to consider the utility of a hybrid of a categorical-dimensional system (Adam, 2013).

An unsolved theoretical question in psychosis is whether symptom data distribution is unidimensional or multidimensional. The statistical model that applies to solve this dimensionality issue is the bifactor solution (Holzinger and Swineford, 1937). After disappearing for many decades, bifactor measurement modelling has been recently rediscovered in psychometrics, including a general factor representing shared variance among all symptoms and a set of specific factors where the remainder of the variance is shared among subsets of symptoms (Reise *et al.*, 2007, Reise, 2012). In psychosis, this resulted in the identification of a more fundamental general, transdiagnostic dimension in addition to the traditional five specific symptom dimensions (Reininghaus *et al.*, 2013, Reininghaus *et al.*, 2016, Shevlin *et al.*, 2017, Reininghaus *et al.*, 2019).

Chapter 3: Methodology

3.1 Summary

The main objective of this PhD project is the investigation of the dimensional structure of psychopathology at FEP and its relationship with genetic and socioenvironmental determinants, focusing on common risk variants and cannabis use. In this chapter, I present overall aims, sample, and methods. In the following chapters (Chapters 4, 5, and 6), each study is illustrated in detail in the form of published or submitted manuscripts.

3.1.1 Aims and hypothesis

1) Examine the transdiagnostic dimensional structure at FEP. I hypothesised that a bifactor model composed of one general psychosis factor and five specific dimensions of positive, negative, disorganization, manic, and depressive symptoms best fitted the covariance among the observed symptoms (Study 1; Chapter 4).
2) Examine the dimensional structure of psychotic experiences in controls representative of the population living in the same areas of the patients with psychosis. I hypothesised that one general psychosis experience factor and three specific dimensions of positive, negative, and depressive psychotic experiences best fitted the covariance among the reported experiences (Study 2; Chapter 5).
3) Examine whether socioenvironmental and context factors explain differences in symptom dimensions regardless of the categorical diagnoses. I hypothesised that being male and not using cannabis, as marker suggestive

of a more early neurodevelopmental impairment in psychosis, would be associated with more negative symptoms (Study 1 and Study 2; Chapters 4 and 5); being part of an ethnic minority and using cannabis, as marker suggestive of more socioenvironmental risk for psychosis, would be instead associated with more positive symptoms (Study 1 and Study 2; Chapters 4 and 5).

4) Examine whether the genetic liability to schizophrenia and bipolar disorder explains differences in symptom dimensions. Regardless of categorical diagnoses, I hypothesised that common variants liability to developing schizophrenia would be associated with more negative symptomatology; and, furthermore, with more positive symptomatology independently from the use of cannabis. Moreover, I hypothesised that, regardless of categorical diagnoses, common variants liability to bipolar disorder would be associated with more manic symptomatology (Study 3; Chapter 6).

3.2 Study design

A multi-site population-based incidence and case-control study [The EUropean Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study], was used for this thesis, which comprises cases with a first episode of psychosis (International Classification of Diseases [ICD]-10 diagnoses F20-29 and F30-33) and controls recruited from 17 sites in six countries (England, the Netherlands, France, Spain, Italy, and Brazil). The catchment areas were intentionally selected to include a mix of urban and rural areas, and different proportions of minority ethnic groups.

3.2.1 Sample

Recruitment and data collection were conducted over a five-year period between 2010 and 2015 in all sites except the Veneto region in Italy. The Veneto sample was part of an earlier study (the Psychosis Incident Cohort Outcome Study [PICOS]; 2005-2007), which used similar methodology as the EU-GEI study, allowing it to be pooled with the main sample.

The incidence sample consisted of 2,774 individuals with a first episode of psychosis. Of the 1,519 individuals that were approached, 1,130 were consented and assessed (41% of the total incidence sample). Main reasons for non-participation were: refusal to participate, language barriers, and exclusion after consenting as they did not meet the age inclusion criteria. In addition, 1,497 population controls were recruited and assessed.

The incidence sample was used for the study 1 (Chapter 4) of this thesis, whereas the case-control sample was used for study 2 and study 3 (Chapters 5 and 6).

3.2.2 Case ascertainment and recruitment

All cases presenting to mental health services in any of the 17 catchment areas with a suspected first episode of psychosis were potentially eligible for inclusion in the study. The inclusion criteria for cases were: a) presence of at least one positive psychotic symptom for at least one day or two negative psychotic symptoms (for at least six months duration) within the time-frame of the study; b) aged between 18 and 64 years; and c) resident within a clearly defined catchment area at the time of their initial presentation. Residence was defined as a minimum of a one night stay at a residential address within the catchment areas. Exclusion criteria were: a) previous contact with specialist mental health services for psychotic

symptoms outside of the study period at each site; b) evidence of psychotic symptoms precipitated by an organic cause (ICD-10: F09); c) transient psychotic symptoms resulting from acute intoxication (F1X.5); d) severe learning disabilities, defined by an IQ less than 50 or diagnosis of intellectual disability (F70 to F79); and, for the case-control study, e) lack of fluency of the primary language at each study site.

Teams of centrally trained researchers regularly screened general adult and specialist mental health services to identity study participants. Only cases that met the criteria based on the symptoms reported in the clinical notes were included in the study. Potential cases were approached when considered appropriate by clinical staff and sought informed consent.

3.2.3 Control recruitment

Inclusion criteria for controls were a) aged between 18 and 64 years; b) resident within a clearly defined catchment area at the time of consent into the study; c) sufficient fluency of the primary language at each study site; and d) no current or past psychotic disorder. A mixture of random and quota sampling was used to select a population-based sample of controls representative of local populations in relation to age, gender, and ethnicity. Quotas for control recruitment were based on the most accurate local demographic data available, and achieved using varying recruitment methods, including: 1) random sampling from lists of all postal addresses; 2) stratified random sampling via GP lists from randomly selected surgeries; and 3) ad hoc approaches (e.g., internet and newspaper adverts, leaflets at local stations, shops, and job centers). Individuals who agreed to participate in the study were screened for a history of psychosis and excluded if reported previous or current

treatment for psychotic symptoms. Those who indicated a possible psychotic symptom in the screening survey, were interviewed further with standardised interviews to establish presence of a psychotic disorder.

3.2.4 Data content

Demographic, clinical, social, psychological, cognitive, and biological data were collected in the EU-GEI study using previously validated questionnaires, tasks, and procedures.

For the purpose of this thesis, environmental exposures and psychopathology were measured using previously validated instruments, and a detailed description is presented in the methods of the subsequent study chapters.

Genetic risk was measured indirectly, using a familial liability score for psychosis, and directly, using DNA extracted from two 9ml non-fasting venous blood samples and/or via saliva samples (Oragene). Samples were genotyped using custom Illumina HumanCoreExome-24 BeadChip genotyping arrays containing probes for 570,038 genetic variants (Illumina Inc., San Diego, CA). Genotype data were called using the GenomeStudio package, transferred into PLINK format for further analysis and underwent quality control based on genotype variants and samples.

3.2.5 Quality assurance and control

Study meetings were regularly arranged prior to and during the study annually, including both principal investigators and core researchers to: 1) guarantee standardised procedures were being implemented; 2) provide instruction; 3) discuss any issues with recruitment; and 4) conduct inter-rater reliability training. The study

was designed to ensure comparable procedures and methods across different sites, with some local adaptation to allow for variations in healthcare provision and health service contact points. The main deviation from protocol was in the Veneto region, Italy, where data were derived from a previous study which used comparable methods, however had a lower upper-age limit of 54.

A technical working committee of the overall EU-GEI study (Work Package 11) trained researchers who were performing the assessments at the outset and throughout the study. Furthermore, an online resource was made available with taped interviews, samples of recordings, and written summaries for staff training purposes. Inter-rater reliability was assessed annually. Researchers were required to attain and maintain a minimum threshold of correct ratings before being allowed to administer the core assessments. Satisfactory levels of inter-rater reliability for the core measurements, ranging from 0.70-0.91, were achieved.

3.2.6 Data management

Data used for the current thesis was collected on paper, stored at each of the participating study centres, and entered locally using an encrypted web-based system, based on a commercial software (4D), which was adapted for the EU-GEI study. In order to minimise data entry errors, information was entered using field codes, restricted to logical values where possible. Blood and/or saliva samples were taken at site-specific clinical research facilities by trained staff and were pseudo-anonymized using a bar code and sent to the Institute of Psychological Medicine and Clinical Neurology at Cardiff University for genotyping. The data resource has undergone a rigorous period of validation checks and cleaning by a small number of experienced researchers. This includes but is not limited to manual checks of

missing data and corroboration of these against the paper files at each of the 17 sites.

3.2.7 Ethical approval

All participants who agreed to take part to the study provided informed, written consent following full explanation of the study. Ethical approval was provided by relevant research ethics committees in each of the study sites.

Chapter 4: Study 1

The core of this paper is the investigation of the structure of psychopathology at FEP, based on the notion that affective and non-affective psychoses are not entirely separate entities and they partly overlap. Thus, in order to identify latent factors that account for the variation and covariation among observed symptoms (i.e. symptom dimensions), I needed to estimate a model where the shared elements (i.e. a unique general factor) and the specific elements (i.e. multiple specific dimensions) may co-exist across the psychosis spectrum. As explained in the introduction, the bifactor structure is a hybrid uni- and multi- dimensional solution which scales general and specific dimensions simultaneously, by modelling in parallel the variance-covariance of the whole symptomatology (general factor) and of subset of symptoms (specific dimensions). The second part of this paper focuses on the examination of clinical and demographic characteristics associated with symptom dimensions in order to confer external validity to the bifactor model and inform research and clinical practice. Table 1 reports the summary of aims and hypotheses for study 1.

Table 1. Summary of aims and hypothesis for study 1

Aims	Hypothesis	Grounds of the hypothesis	Analytic approach
To identify latent factors of psychopathology at FEP	A bifactor solution accounts for the variance-covariance among symptoms of psychosis better than alternative solutions	Epidemiological, clinical, and biological studies indicated lack of neat boundaries between categories of psychotic disorders (Owen and O'Donovan, 2017, Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019).	Multidimensional item response modelling in M*plus.*

		The bifactor solution is appropriate for modelling psychosis symptoms (Reise *et al.*, 2007, Reininghaus *et al.*, 2016)	
To examine the relationship between latent factors with demographic and context determinants	Positive symptoms are more common in minority ethnic groups	A disadvantageous social context may exacerbate positive symptoms (Janssen *et al.*, 2003)	Multiple linear regression in STATA14.
	Negative symptoms are associated with indices of neurodevelopmental impairment in psychosis	Early deficits in neuro- and social cognition may contribute to exacerbation of primary negative symptoms (Murray *et al.*, 2017a)	

4.1 Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study

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Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study

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Abstract

Background. The value of the nosological distinction between non-affective and affective psychosis has frequently been challenged. We aimed to investigate the transdiagnostic dimensional structure and associated characteristics of psychopathology at First Episode Psychosis (FEP). Regardless of diagnostic categories, we expected that positive symptoms occurred more frequently in ethnic minority groups and in more densely populated environments,

and that negative symptoms were associated with indices of neurodevelopmental impairment.
Method. This study included 2182 FEP individuals recruited across six countries, as part of the EUropean network of national schizophrenia networks studying Gene–Environment Interactions (EU-GEI) study. Symptom ratings were analysed using multidimensional item response modelling in *Mplus* to estimate five theory-based models of psychosis. We used multiple regression models to examine demographic and context factors associated with symptom dimensions.
Results. A bifactor model, composed of one general factor and five specific dimensions of positive, negative, disorganization, manic and depressive symptoms, best-represented associations among ratings of psychotic symptoms. Positive symptoms were more common in ethnic minority groups. Urbanicity was associated with a higher score on the general factor. Men presented with more negative and less depressive symptoms than women. Early age-at-first-contact with psychiatric services was associated with higher scores on negative, disorganized, and manic symptom dimensions.
Conclusions. Our results suggest that the bifactor model of psychopathology holds across diagnostic categories of non-affective and affective psychosis at FEP, and demographic and context determinants map onto general and specific symptom dimensions. These findings have implications for tailoring symptom-specific treatments and inform research into the mood-psychosis spectrum.

Introduction

Current nosology classifies the observed manifestations of psychosis into two main categories of non-affective (e.g. schizophrenia, schizoaffective disorder) and affective psychosis (e.g. bipolar and major depressive disorders with psychotic features) (World Health Organization, 1992; American Psychiatric Association, 2013). However, the scientific accessibility of discrete 'natural disease entities' in psychiatry has been questioned since Kraepelin's original distinction between dementia praecox and manic-depressive psychosis (Kraepelin, 1899; Murray *et al.*, 2004; Craddock and Owen, 2005; Hoff, 2017). On this basis, it has been proposed, and is now widely accepted, that the categorical classification system alone is too reductionist to explain the complexity of psychotic phenomena (Van Os *et al.*, 1999; Linscott and van Os, 2010). Various evidence-based perspectives might support a scheme incorporating symptom dimensions in psychotic disorders, as a possible approach to address the following limitations of categorical distinctions.

First, the dichotomous model of non-affective and affective psychosis does not fit the cases presenting with both prominent mood and psychotic symptoms. This is testified by the notion of a third category of schizoaffective disorder (Kasanin, 1933), which nevertheless implies further nosological challenges (Abrams *et al.*, 2008).

In addition, if criteria-based classification systems could identify genuine disorders within the psychosis spectrum, the diagnostic overlap would be relevant to only a few patients. On the contrary, there is a large comorbidity index between schizophrenia, schizoaffective, bipolar, and major depressive disorders (Laursen *et al.*, 2009; Upthegrove *et al.*, 2017). Similarly, the 10-year outcomes of the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP-10) study showed that diagnoses within psychosis other than schizophrenia at baseline tend to be unstable over time (Heslin *et al.*, 2015).

Also, the dichotomous model is neither consistent with family studies showing familial co-aggregation of non-affective and affective psychosis (Cardno *et al.*, 2002; Lichtenstein *et al.*, 2009; Chou *et al.*, 2017) nor with the accumulated evidence from genome-wide association studies that genetic risk is in part shared among schizophrenia, bipolar disorder, and major depressive disorder (International Schizophrenia Consortium *et al.*, 2009; Demjaha *et al.*, 2011; Cardno and Owen, 2014; O'Donovan and Owen, 2016; Power *et al.*, 2017).

Last, several studies show the efficacy of agents which impact on dopamine signalling in the treatment of both non-affective and affective symptoms. For example, antipsychotics antagonise D2-receptor functioning and are used in bipolar disorder and schizophrenia (Post, 1999; Taylor *et al.*, 2015), and clozapine is prescribed for both treatment-resistant bipolar disorder and schizophrenia (Li *et al.*, 2015; Goodwin *et al.*, 2016; Howes *et al.*, 2016). These findings suggest that dopamine dysregulation may contribute to both positive and manic symptoms, as supported by recent positron emission tomographic findings (Jauhar *et al.*, 2017).

Taken together, the above evidence challenges the binary categorization of non-affective and affective psychosis, enhancing research into non-categorical approaches. Pioneering studies using factor analysis examined associations among non-affective symptoms in schizophrenia and showed that these symptoms segregated in three groups (Liddle, 1987); however, these groups could not accommodate the whole symptom diversity in schizophrenia (Kay and Sevy, 1990). Thus, psychopathology models including also depressive and manic factors were proposed and replicated in schizophrenia (Lindenmayer *et al.*, 1994; Salokangas, 1997; Wickham *et al.*, 2001; Wallwork *et al.*, 2012). This type of structure was likewise confirmed in psychotic disorders (Salokangas, 2003; Dikeos *et al.*, 2006; Demjaha *et al.*, 2009), and in a sample of bipolar patients (Lindenmayer *et al.*, 2008). Hence, its validity across the spectrum of non-affective and affective psychosis has been consistently supported.

Recent findings suggest a more fundamental general, transdiagnostic dimension encompassing non-affective and affective symptoms, in addition to five specific symptom dimensions (Reininghaus *et al.*, 2013; Reininghaus *et al.*, 2016; Shevlin *et al.*, 2017). This conceptualization statistically reflects a bifactor model, with one general factor representing shared variance among all symptoms, and a set of specific factors where the remainder of the variance is shared among subsets of symptoms (Reise *et al.*, 2007). This is the first study set to investigate, in an incidence sample of First Episode Psychosis (FEP) patients: (1) whether the general psychosis dimension holds across

diagnostic categories of non-affective psychosis (i.e. schizophrenia, schizoaffective disorder) and affective psychosis (i.e. bipolar and major depressive disorder with psychotic features); (2) whether formation of specific symptom dimensions is justified in addition to a general psychosis dimension; and (3) the association of demographic characteristics (i.e. age, gender, ethnicity), social context (i.e. urbanicity), and clinical factors (i.e. diagnosis) with general and specific psychosis dimensions.

The hypotheses underlying the third aim, based on the existing literature, were:

(a) Positive symptoms would be more common in ethnic minority groups and in people living in more densely populated environments (van Os *et al.*, 2001, Janssen *et al.*, 2003).
(b) Negative symptoms would be associated with indices suggestive of neurodevelopment impairment in psychosis (Limosin, 2014; Patel *et al.*, 2015), such as being a man or having an early age at onset.

Methods

Sample design and procedures

Individuals suffering from their FEP were recruited between 2010 and 2015 as part of the large EUropean network of national schizophrenia networks studying Gene–Environment Interactions (EU-GEI) study (http://www.eu-gei.eu). Specifically, FEP individuals were recruited as part of the 'Functional Enviromics' work package, which consisted of an incidence and a case-sibling-control study conducted across six countries with the aim to investigate clinical, genetic, and environmental interaction in the development of psychotic disorders.

The study had 17 catchment areas, including urban and less urban populations: Southeast London, Cambridgeshire and Peterborough (England); central Amsterdam, Gouda and Voorhout (the Netherlands); part of the Veneto region, Bologna municipality, city of Palermo (Italy); 20th arrondissement of Paris, Val-de-Marne, Puy-de-Dôme (France); Madrid (Vallecas), Barcelona, Valencia, Oviedo, Santiago, Cuenca (Spain); and Ribeirão Preto (Brazil).

Participants

We screened all subjects who were referred to mental healthcare services with a suspicion of psychosis. The ascertainment period of cases ranged from 12 months in London to 48 months in Val-de-Marne and Bologna, with a median of 25 months. In each site, a psychiatrist experienced in epidemiology research oversaw the local team, which was centrally trained to minimize non-differential recruitment bias in the different healthcare systems. Written consent was obtained from the subjects who agreed to take part of the case-sibling-control study. For incidence-only cases, local research ethics committees approved the extraction of demographics and clinical information from patient records. More detailed information is available on the EU-GEI core paper on the incidence rates of schizophrenia and other psychotic disorders (Jongsma *et al.*, 2018).

Patients were included in the current study if they met the following criteria during the recruitment period: (a) aged between 18 and 64 years; (b) presentation with a clinical diagnosis for an untreated FEP, even if longstanding [International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes F20-F33]; (c) resident within the catchment area at FEP. Exclusion criteria were: (a) previous contact with psychiatric services for psychosis; (b) psychotic symptoms with any evidence of organic causation; and (c) transient psychotic symptoms resulting from acute intoxication (ICD-10: F1*x*.5).

Measures

Data on age, gender, and ethnicity was collected using a modified version of the Medical Research Council Sociodemographic Schedule (Mallett, 1997). Ethnicity was defined as self-reported. Country of heritage or birth was used as a proxy for ethnicity in people of a North African background. The OPerational CRITeria (OPCRIT) system (McGuffin *et al.*, 1991; Williams *et al.*, 1996) was used by centrally trained investigators, whose reliability was assessed throughout the study ($\kappa = 0.7$). The OPCRIT system allows to: (1) assess the pre-morbid history and current mental state; and (2) establish the diagnosis of psychotic disorders based on algorithms for several diagnostic classification systems. It consists of a checklist which can be filled using different sources, e.g. case records or clinical interviews. Fifty-nine items relate to the mental state examination. We used diagnoses based on Research Diagnostic Criteria (RDC) (Spitzer *et al.*, 1978), since this classification system provides a better representation of schizoaffective disorder, which is a common presentation in clinical practice. OPCRIT RDC-based diagnoses have a good-to-excellent agreement with best-estimate consensus diagnostic procedures (Craddock *et al.*, 1996). In each catchment area, population density was computed as a number of inhabitants per square kilometre, based on official population estimates.

Statistical analysis

Psychopathology items were dichotomized as 0 'absent' or 1 'present'. In order to ensure sufficient covariance coverage for item response modelling, we used the items with a valid frequency of 'present' $\geqslant$10% in our sample, which included individuals with $\leqslant$20 missing values in the psychopathology rating. OPCRIT data used in the analysis contained missing values, which we assumed to be missing at random, allowing for the maximum likelihood estimator to provide unbiased estimates. We performed multidimensional item response modelling in *Mplus*, version 7.4 (Muthén and Muthén, 2012) to estimate unidimensional, multidimensional, bifactor, and second-order models of psychosis.

Extending previous analyses of OPCRIT data in individuals with enduring psychosis (Reininghaus *et al.*, 2016), we estimated five alternative item-response models (online Supplementary Fig. S1): (a) a unidimensional model with one unique general factor (model A), which is consistent with the pre-Kraepelinian unitary concept of psychosis (Berrios and Beer, 1994); (b) a multidimensional model with five uncorrelated specific factors of positive, negative, disorganization, manic, and depressive symptoms (model B); (c) a multidimensional model with five correlated specific factors (model C), which, together with model B, is consistent with the pentagonal psychosis model (van Os and Kapur, 2009); (d) a bifactor model with one general latent factor along with five uncorrelated specific factors (model D) (Reininghaus *et al.*, 2016); and (e) a hierarchical model with five first-order specific factors and one general second-order factor (model E), which, as model D, is consistent with the notion of a transdiagnotic spectrum of non-affective and affective psychosis (Craddock and Owen, 2005; Reininghaus *et al.*, 2016). Some previous

OPCRIT exploratory analysis showed a combined negative/disorganization dimension (Serretti *et al.*, 2001; Fanous *et al.*, 2005). We did not have a strong theoretical rationale for testing such a structure in a confirmatory analysis. By contrast, we considered specific negative symptoms as a clinically observable marker of neurodevelopmental impairment in psychosis (Limosin, 2014).

The five models were compared using Log-Likelihood (LL), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Sample-size Adjusted BIC (SABIC) as model fit statistics. For the model showing the best fit, we calculated reliability and strength indices, such as McDonald's omega (ω), omega hierarchical (ω_H), and index H. Coefficient ω is an estimate of the proportion of common variance accounted by general and specific symptom dimensions. Coefficient ω_H is an estimate of the proportion of reliable variance accounted by the general dimension, treating variability in scores due to specific dimensions as measurement error (Rodriguez *et al.*, 2016*b*). Ωh formula can be extended to each specific factor, i.e. treating variability in scores due to the general factor as a measurement error, to compute omega hierarchical for subscales. Based on omega and omega hierarchical coefficients, which can vary from 0 to 1, we computed the ratios of ω/ω_H, namely the relative omega, as the amount of reliable variance explained in the observed scores attributable to (1) the general factor independently from the specific symptom dimensions, and (2) each specific symptom dimension independently from the general factor. To estimate the extent to which symptom dimensions were represented by their own set of OPCRIT items and their replicability across studies, we computed the construct reliability index H (Hancock and Mueller, 2001). The index H ranges from 0 to 1, with values closer to 1 indicating better reliability and replicability (Rodriguez *et al.*, 2016*a*). Quantitative scores for all symptom dimensions were calculated using the 'FSCORES' function in *Mplus*.

Further, we examined the diagnostic classification accuracy based on general and specific symptom dimension scores using multinomial receiver operating characteristic (ROC) analysis in STATA 14 (StataCorp, 2015). In addition, we performed a sensitivity analysis, examining subjects with item ratings based on face-to-face interview and based on clinical records separately.

We used multiple linear regression to examine the association between factor scores of general and/or specific psychosis dimensions as the outcome variable and demographic variables, including gender, age-at-first-contact with psychiatric services, ethnicity, and diagnosis as covariates. Country and assessment method were treated as a priori confounders.

To examine the individual-level effect of urbanicity on symptom dimension scores, standardized population density values were used as a continuous independent variable, while controlling the analysis for gender, age-at-first-contact, ethnicity, diagnosis, and assessment method. Sensitivity analysis included post-hoc multiple regressions within each country, where population density was dichotomized at its median as a dummy variable for urbanicity.

Results

Sample characteristics

We identified 2774 treated incidence cases of psychosis (Jongsma *et al.*, 2018), of whom 2182 had (complete or missing at random) OPCRIT data available for analysis under the provision of local research ethics committees (Table 1). OPCRIT item ratings were completed based on face-to-face assessment for 51% ($n = 1112$) and based on clinical records for 49% ($n = 1070$) of the sample. The sample prevalence of psychotic symptoms is presented in Supplementary Table S1.

Fifty-seven per cent of FEP were men. Subjects were mostly people of a White ethnicity. Other main ethnic groups included Black African and Black Caribbean, North African, Mixed, and Asian. Mean age-at-first-contact with psychiatric services was 32.1 years; this was lower in men ($M = 30.1$) compared with women ($M = 34.7$; $t = -9.6$, $p < 0.001$). Age-at-first-contact differed across ethnic groups, with individuals of Black ethnicity ($M = 29$) being younger than individuals of White ethnicity ($M = 32.7$; $F = 7.72$, $p < 0.001$). The most common RDC-based diagnosis was broad or narrow schizophrenia (38.6%), followed by schizoaffective disorders (35%), unspecified non-organic psychotic disorder (16.3%), bipolar disorder (5.9%), and psychotic depression (4.2%).

Symptom dimensions in the EU-GEI sample

The bifactor model was the best fit for the OPCRIT symptom data compared with all other models, as consistently indicated by each of the model fit statistics (Table 2), and explained 54% of the total variance.

Figure 1 shows that, within the bifactor model, general and specific dimensions accounted for 93% of the common variance. Overall, statistical indices derived from the bifactor model suggest that its explained variance was due to individual differences in both general and specific symptom dimensions, which therefore might complement each other in reflecting the psychopathological structure at FEP. This is illustrated by the relative omega coefficients, which, for example, showed that 47% of the reliable variance was due to the general factor when partitioning out the variability in scores due to the specific factors (Fig. 1). High H values were consistently observed for all latent factors, indicating that they were well defined, and that the bifactor model had high reliability and replicability (Fig. 1). Sensitivity analysis showed that the bifactor model was the best fit for the OPCRIT data in both the assessment methods (online Supplementary Tables S2.1 and S2.2).

Symptom dimensions and item factor loadings

Table 3 shows standardized factor loadings for the bifactor model. On the general dimension, a positive factor loading was observed for all OPCRIT items with statistically significant loadings. In addition, the magnitude of factor loadings of items on the general dimension was small, except for some manic/delusional items for which loadings of moderate magnitude were observed. On the specific dimensions, most of the items showed moderate to strong positive loadings. Finally, latent factor scores were strongly and positively associated with simplified weighted OPCRIT sum scores for use in clinical practice (online Supplementary Table S3).

Symptom dimensions and categorical diagnoses

Findings from regression analyses are shown in Table 4 and predicted symptom dimension scores for each RDC-based diagnostic category are reported in Fig. 2. Compared with bipolar disorder, factor scores for the positive dimension were moderately higher in schizophrenia and schizoaffective disorder; factor scores for the negative dimension were moderately higher in schizophrenia,

Table 1. Demographic and clinical characteristics of the sample included in the factor analysis

Characteristics	*N* (%) 2182	Differences by assessed method[a] Test statistics	Differences by country[b] Test statistics
Age			
Mean (s.d.)	32.1 (11.2)	$t(2180) = -5.57$; $p < 0.001$	$F(5,2176) = 7.42$; $p < 0.001$
Median (IQR)	30 (23–40)	Kruskal–Wallis $\chi^2(1) = 29.19$; $p < 0.001$	Kruskal–Wallis $\chi^2(5) = 37.4$; $p < 0.001$
Gender[c]			
Male	1247 (57.2)	$\chi^2(1) = 14.73$; $p < 0.001$	$\chi^2(5) = 16.59$; $p < 0.01$
Ethnicity[d]			
White	1245 (57.1)	$\chi^2(4) = 69.06$; $p < 0.001$	$\chi^2(20) = 535.15$; $p < 0.001$
Black	231 (10.6)		
Mixed	168 (7.7)		
Asian	79 (3.6)		
North African	61 (2.8)		
Other and missing self-reported	398 (18.2)		
Research Domain Criteria Diagnosis[e]			
Bipolar disorder	129 (5.9)	$\chi^2(4) = 19.25$; $p = 0.001$	$\chi^2(20) = 137.47$; $p < 0.001$
Major depression with psychotic features	92 (4.2)		
Schizophrenia spectrum	842 (38.6)		
Schizoaffective disorder	764 (35)		
Unspecified psychosis	355 (16.3)		

[a]Psychopathology assessment methods included face-to-face interview or review of clinical notes.
[b]Study countries were England, the Netherlands, France, Spain, Italy, and Brazil.
[c]29 missing values excluded from tabulation and age analysis.
[d]Other and missing self-reported groups excluded from ethnicity analysis.
[e]Schizophrenia spectrum encompassed Broad Schizophrenia (*N* = 194) and Narrow Schizophrenia (*N* = 648); Schizoaffective disorder encompassed Schizoaffective/manic (*N* = 112); Schizoaffective/depressive (*N* = 566); Schizoaffective/bipolar (*N* = 86).

schizoaffective and psychotic depression; and factor scores for the depressive dimension were markedly higher in psychotic depression and schizoaffective disorder. Bipolar disorder showed the highest factor scores for the manic and the general dimensions. Dimension scores based on ICD diagnostic categories are presented in Supplementary Fig. S2 and Supplementary Table S4.

Finally, ROC analysis showed that classification accuracy into RDC categories based on general and specific symptom dimension scores was markedly higher for patients with psychopathology rating based either on face-to-face interview (95% CI 0.54–0.63) or case note review (95% CI 0.56–0.65), compared with a classification by chance (95% 0.32–0.41). Moreover, symptom dimensions showed similar diagnostic classification accuracy across countries (online Supplementary Figs S3.1 and S3.2).

Symptom dimensions by gender, age-at-first-contact, and ethnicity

Findings on factor scores by gender, age-at-first-contact, and ethnicity, are shown in Fig. 2 and Table 4. Early age-at-first-contact was associated with higher scores for the general, negative, disorganized, and manic symptom dimensions, and with lower scores for the depressive symptom dimension. Men showed fewer depressive symptoms and more negative symptoms than women, even after adjusting the analysis for several confounders. Table 4 further shows that participants of Black and North African ethnicity presented with higher scores on the positive symptom dimension compared with an individual of White ethnicity. Finally, higher scores for the disorganization dimension and lower scores for the depressive dimension were observed in Black compared with White ethnicity. Noteworthy, the magnitude of the effect was small for all the results.

Symptom dimensions by urbanicity

A moderate positive association was observed for more densely populated environments and the general dimension score. Table 4 further shows a weaker positive association between population density and specific negative, disorganization, and manic symptom dimensions. Post-hoc analysis of symptom dimensions within countries showed that positive symptoms were more common in urban study sites in the UK (i.e. London *v.* Cambridge), whereas a negative association was observed in Spain (online Supplementary Table S5).

Discussion

Principal findings

This is the first study on general and specific symptom dimensions in an incidence sample of psychosis. First, we found in our FEP sample that manic and delusional symptoms primarily underlie the identified general psychosis factor across diagnostic categories of non-affective and affective psychosis. Second, findings showed that specific dimensions of positive, negative,

Table 2. Model fit statistics of unidimensional, multidimensional, bi-factor, and second-order models

	Full information fit statistics[a]			
Sample size: 2182	LL	AIC	BIC	SABIC
A – Unidimensional Model	−54809	109813	110370	110059
B – Multidimensional Model (five uncorrelated factors)	−50645	101487	102044	101733
C – Multidimensional Model (five correlated factors)	−50439	101095	101709	101365
D – Bifactor Model (one general factor and five specific uncorrelated factors)	−49710	99713	100549	100082
E – Hierarchical Model (five first-order specific correlated factors and one second-order general factor)	−50608	101420	102000	101676

LL, log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SABIC Sample-size Adjusted Bayesian Information Criterion.
[a]A difference of 10 in AIC, BIC and SABIC is considered important. Lower values indicate a statistically better model fit.

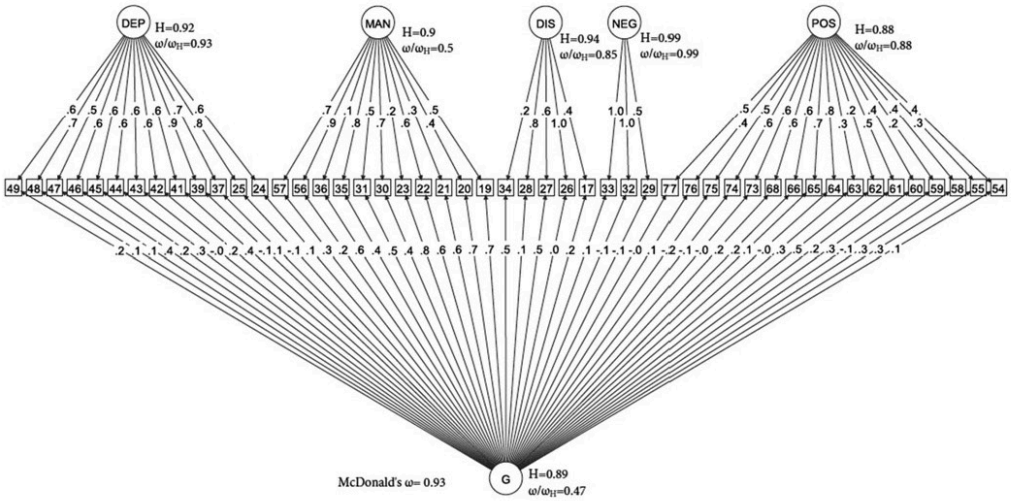

Fig. 1. Bifactor model. (□) Observed variables (No. of OPCRIT items); (○) Unobserved variables (latent factors); (→) standardized item loading estimation onto latent factors; G, general psychosis factor; specific symptom factors: DEP, depression; MAN, mania; DIS, disorganization; NEG, negative; POS, positive. Reliability and strength estimates: *H* = construct reliability index; ω = McDonald omega; ω_H = hierarchical omega; ω/ω_H = Relative omega. Explanatory note: McDonald's ω is an estimate of the proportion of the common variance accounted by general and specific symptom dimensions. Relative omega (ω/ω_h) is the amount of reliable variance explained in the observed scores attributable to (1) the general factor independently from the specific symptom dimensions, and (2) each specific symptom dimension independently from the general factor. *H* is an index of the quality of the measurement model based on the set of OPCRIT items for each symptom dimension. Index *H* can range from 0 to 1, with values closer to 1 indicating a better construct reliability and replicability across studies.

disorganized, manic and depressive symptoms are complementary to the general dimension. Third, general and specific symptom dimensions discriminated well between diagnoses of psychotic disorders. Forth, positive symptoms were more common among individuals of Black and North African ethnicity. Fifth, there was some evidence that early age-at-first-contact was associated with higher scores for several dimensions, such as of negative, disorganised and manic symptoms. Sixth, men presented with more negative and less depressive symptoms than women. Finally, higher scores for the general dimension were observed for individuals living in urban neighbourhoods.

Limitations

Before interpreting our findings, we must consider potential limitations. Symptoms were rated with a semi-structured face-to-face interview or from case note review. Still, study investigators underwent a specific and centrally organized training for OPCRIT and demonstrated good inter-rater reliability for individual item ratings; moreover, OPCRIT is a tool specifically designed to allow use with different sources (McGuffin *et al.*, 1991; Cardno *et al.*, 1996; Rucker *et al.*, 2011). However, we found consistently lower symptom ratings using case note review compared with face-to-face interviews. It is possible that clinicians failed to record all symptoms; alternatively, patients presenting with less severe psychopathology had a shorter contact with services, and therefore less chances to be interviewed by researchers. Whether or not differences in ratings are genuine or a surrogate of different sources of item ratings, we treated this potential bias as artificial confounding of our findings and adjusted all analyses for the type of assessment method. On the other hand, the use of an incidence sample allowed the best possible approximation of the true

Table 3. Standardized factor loadings in the bifactor model

OPCRIT item	Item no.	Factor	Specific factor loading	General factor loading	Communalities
Persecutory delusions	54	POS	0.36***		0.14
Well organized delusions	55	POS	0.27***	0.34***	0.19
Delusions of influence	58	POS	0.43***	0.33***	0.29
Bizarre delusions	59	POS	0.21***		0.05
Widespread delusions	60	POS	0.42***	0.29***	0.26
Delusions of passivity	61	POS	0.49***		0.27
Primary delusional perception	62	POS	0.23***	0.51***	0.32
Other primary delusions	63	POS	0.30***	0.31***	0.19
Delusions & hallucinations last for 1 week	64	POS	0.81***		0.65
Persecutory/jealous delusions & hallucinations	65	POS	0.66***		0.45
Thought insertion	66	POS	0.60***		0.38
Thought broadcast	68	POS	0.60***	0.24***	0.41
Third person auditory hallucinations	73	POS	0.61***		0.37
Running commentary voices	74	POS	0.62***		0.39
Abusive/accusatory/persecutory voices	75	POS	0.54***		0.33
Other (non-affective) auditory hallucinations	76	POS	0.42***		0.19
Non-affective hallucinations in any modality	77	POS	0.51***		0.26
Negative formal thought disorder	29	NEG	0.54***		0.30
Restricted affect	32	NEG	1.00***		1.00
Blunted affect	33	NEG	0.98***		0.97
Bizarre behaviour	17	DIS	0.42***	0.21***	0.23
Speech difficult to understand	26	DIS	0.96***		0.93
Incoherent	27	DIS	0.62***	0.47***	0.60
Positive formal thought disorder	28	DIS	0.84***		0.72
Inappropriate affect	34	DIS	0.23***	0.46***	0.27
Excessive activity	19	MAN	0.53***	0.73***	0.82
Reckless activity	20	MAN	0.36***	0.67***	0.58
Distractibility	21	MAN	0.29***	0.60***	0.45
Reduced need for sleep	22	MAN	0.55***	0.56***	0.61
Agitated activity	23	MAN	0.16***	0.76***	0.59
Pressured speech	30	MAN	0.74***	0.43***	0.73
Thoughts racing	31	MAN	0.54***	0.49***	0.53
Elevated mood	35	MAN	0.85***	0.41***	0.89
Irritable mood	36	MAN	0.12**	0.55***	0.32
Increased self esteem	56	MAN	0.87***	0.24***	0.81
Grandiose delusions	57	MAN	0.67***	0.30***	0.54
Slowed activity	24	DEP	0.55***		0.31
Loss of energy/tiredness	25	DEP	0.80***		0.64
Dysphoria	37	DEP	0.74***		0.55
Loss of pleasure	39	DEP	0.87***		0.76
Poor concentration	41	DEP	0.62***	0.42***	0.56
Excessive self-reproach	42	DEP	0.60***		0.38
Suicidal ideation	43	DEP	0.55***		0.31

(*Continued*)

Table 3. (*Continued.*)

OPCRIT item	Item no.	Factor	Specific factor loading	General factor loading	Communalities
Initial insomnia	44	DEP	0.65***	0.32***	0.53
Middle insomnia (broken sleep)	45	DEP	0.65***	0.25***	0.48
Early morning waking	46	DEP	0.56***	0.39***	0.46
Excessive sleep	47	DEP	0.46***		0.23
Poor appetite	48	DEP	0.69***		0.48
Weight Loss	49	DEP	0.56***	0.20***	0.35

General, general psychosis factor; specific symptom dimensions: DEP, depression; MAN, mania; DIS, disorganisation; NEG, negative; POS, positive. Only loadings ⩾0.2 for the general factor are shown for simplicity. Significance: *** = $p < 0.001$; ** = $p < 0.01$.

distribution of psychosis symptoms at FEP, which may have reduced potentially inflated presence of positive and negative symptoms in previous studies conducted in hospital settings (Allardyce *et al.*, 2007). Also, OPCRIT does not cover some relevant aspects of negative symptoms related to passive social withdrawal, lack of motivation, and difficulties in abstract/symbolic thinking. Consequently, we constructed a narrow negative symptom dimension with three items. Finally, some authors have argued that, in a bifactor model, the general factor may be difficult to interpret and in general may overfit the data (Bonifay *et al.*, 2016). However, the bifactor model allows solutions to dimensionality issues that arise when the conceptual breadth of a construct cannot be fully determined (Reise *et al.*, 2007), as is likely to be the case for the construct of psychosis, which, in the past, has been considered as unidimensional and multidimensional at the same time. For example, the bifactor model discerns each specific symptom dimension from the common item effect, which is captured by the general dimension, thus allowing an accurate evaluation of the unique contribution of each subset of symptoms. Last, this solution provides crucial information which cannot be determined from the other models, i.e. how much of the phenotypic variance that we aim to measure is due to a unidimensional construct *v.* a multidimensional construct of psychosis. Hence, it was a suitable model for addressing dimensionality issues for psychosis and generating reliable phenotypes.

Comparison with previous research

In our study, the bifactor model of psychopathology best explained the observed symptoms at FEP compared with unidimensional and multidimensional models. Our findings are consistent with, and extend, previous research on psychotic symptoms in people with enduring psychotic disorders (Reininghaus *et al.*, 2013; Reininghaus *et al.*, 2016) and the general population (Shevlin *et al.*, 2017) to a multinational incidence sample of FEP. They provide further evidence that non-affective and affective psychotic disorders lie on a common mood-psychosis spectrum (Murray *et al.*, 2004). In addition, we provided the first evidence in psychosis that a bifactor solution shows better model fit statistics compared with a second-order hierarchical solution. However, compared with findings in enduring psychosis (Reininghaus *et al.*, 2016), we found a less specific general psychopathology factor with more general disturbances and affective features. As illnesses develop, the non-affective psychotic phenomena may become more and affective features less prominent.

We found some evidence of gender differences in symptom dimension scores. Men showed less depressive symptoms and more negative symptoms compared with women. This finding is consistent with other studies in stable schizophrenia (Shtasel *et al.*, 1992; Roy *et al.*, 2001; Galderisi *et al.*, 2012), first episode psychotic disorder (Morgan *et al.*, 2008), and the general population (Maric *et al.*, 2003). In our sample, we also showed that early age-at-first-contact was associated with a higher level of general and specific psychopathology. Notably, it has been proposed that gender-related and symptom profiles differences in psychosis may be suggestive of different neurodevelopmental trajectories (Castle and Murray, 1991; Seeman, 1997; Riecher-Rössler and Häfner, 2000).

We further found that symptom dimensions vary in terms of ethnicity. Consistent with a previous report (Kirkbride *et al.*, 2016), we provided evidence that people of Black ethnicity presented at FEP with more positive and disorganized symptoms and fewer depressive symptoms compared with people of White ethnicity. Moreover, in line with another study (Veling *et al.*, 2007), we found in our sample that the North African group presented at FEP with more positive symptoms compared with people of White ethnicity. It has been debated whether similar findings reflect true differences in symptom presentation or instead result from raters being more likely to overrate symptoms in the context of ethno-cultural diversity (Mukherjee *et al.*, 1983; Hutchinson *et al.*, 1999; Barrio *et al.*, 2003; Arnold *et al.*, 2004; Vega and Lewis-Fernandez, 2008). Recent studies using standardized procedures for assessing symptomatology blind to ethnicity have suggested that misdiagnosis or rating bias cannot account for differences across ethnic groups (Morgan *et al.*, 2010). However, we must remain cautious in interpreting these results.

We showed that high population density is positively associated with the general and specific disorganized, negative and manic dimensions. In our multinational sample, we were not able to replicate previous findings on the relationship between urbanicity and the positive dimension (Kirkbride *et al.*, 2007). Nevertheless, stratified analysis by country was consistent with the previously reported association between urbanicity and positive symptoms in the UK. The relationship between urbanicity and a higher incidence of psychotic disorders is well-established (Vassos *et al.*, 2012). However, it has been found to show non-linearity (Kirkbride *et al.*, 2017), which implies that the effect of urbanicity may depend on exposure to additional socio-environmental factors associated with urban contexts, for example cannabis use (Kuepper *et al.*, 2011) and childhood adversities (Frissen *et al.*, 2015). Similarly, our findings support the

Table 4. Symptom dimension scores by sociodemographic, categorical diagnosis, and social context variables

	General B (95% CI)	Positive B (95% CI)	Negative B (95% CI)	Disorganization B (95% CI)	Manic B (95% CI)	Depressive B (95% CI)
Women *v.* Men[a]	0.01 (−0.07 to 0.09)	0.01 (−0.08 to 0.1)	−0.12*** (−0.21 to 0.23)	0 (−0.08 to 0.1)	0 (−0.09 to 0.08)	0.1** (0.02 to 0.17)
Age at first contact[a]	−0.01* (−0.09 to −0.01)	−0.02 (−0.06 to 0.03)	−0.05** (−0.1 to −0.01)	−0.09*** (−0.14 to −0.05)	−0.1*** (−0.14 to −0.06)	0.04* (0.01 to 0.08)
Ethnicity[a]						
Black *v.* White	0.07 (−0.06 to 0.19)	0.19** (0.04 to 0.33)	0.01 (−0.14 to 0.15)	0.14* (0.01 to 0.28)	0.03 (−0.1 to 0.16)	−0.22*** (−0.34 to −0.1)
Mixed *v.* White	0.02 (−0.12 to 0.17)	0 (−0.16 to 0.17)	0.1 (−0.07 to 0.27)	0.18* (0.02 to 0.34)	0.06 (−0.09 to 0.21)	−0.1 (−0.25 to 0.03)
Asian *v.* Withe	−0.06 (−0.25 to 0.13)	0.11 (−0.1 to 0.33)	−0.05 (−0.28 to 0.18)	0.07 (−0.13 to 0.28)	0.01 (−0.19 to 0.21)	−0.08 (−0.27 to 0.1)
North African *v.* White	−0.02 (−0.24 to 0.2)	0.32** (0.07 to 0.57)	−0.22 (−0.48 to 0.04)	−0.05 (−0.29 to 0.2)	−0.17 (−0.4 to 0.06)	0.05 (−0.16 to 0.27)
Diagnosis[a]						
Schizophrenia *v.* Bipolar	−0.78*** (−0.96 to −0.6)	0.9*** (0.69 to 1.1)	0.53*** (0.32 to 0.75)	0.24* (0.06 to 0.45)	−1.7*** (−1.88 to −1.51)	0.78 (−0.1 to 0.25)
Schizoaffective disorder *v.* Bipolar	−0.47*** (−0.65 to −0.29)	0.94*** (0.73 to 1.14)	0.59*** (0.37 to 0.8)	0.3** (0.1 to 0.5)	−1.33*** (−1.52 to −1.15)	0.97*** (0.8 to 1.14)
Major Depression *v.* Bipolar	−1.16*** (−1.42 to −0.91)	−0.24 (−0.52 to 0.05)	0.72*** (0.42 to 1.02)	−0.23 (−0.5 to 0.05)	−1.95*** (−2.21 to −1.69)	1.54*** (1.3 to 1.79)
Unspecified Functional Psychosis *v.* Bipolar	−0.99*** (−1.19 to −0.8)	0.36** (0.14 to 0.58)	0.5*** (0.27 to 0.73)	−0.06 (−0.27 to 0.15)	−1.67*** (−1.87 to −1.47)	0.3** (0.11 to 0.49)
Urban *v.* less urban[b]	0.3*** (0.24 to 0.36)	−0.03 (−0.1 to 0.03)	0.12** (0.05 to 0.19)	0.08** (−0.02 to 0.14)	0.01 (−0.06 to 0.06)	0.02 (−0.04 to 0.07)

B, unstandardised regression coefficient; CI, confidence interval.
[a]Covariates in multiple models were gender, age, ethnicity, diagnosis, study country, and type of assessment method (interview *v.* case records).
[b]Population density analysis was adjusted for gender, age, ethnicity, diagnosis, and type of assessment method (interview *v.* case records).

hypothesis that urban environment does not have a dimension-specific effect and may act to confer risk for different psychopathological outcomes in psychosis (van Os *et al.*, 2002). Noteworthy, similar findings have been reported in the general population (van Os *et al.*, 2001), which may require future studies to consider the additive interaction between putative risk factors for psychosis and urbanicity.

Implications

In the context of a general effort to move away from DSM and ICD categories (Demjaha *et al.*, 2009; Reininghaus *et al.*, 2016; Kotov *et al.*, 2017; Van Dam *et al.*, 2017; Whalen, 2017; Zachar and Kendler, 2017), we found evidence that supports, and may inform, the use of dimensional measures in the field of psychosis. In our sample, the bifactor model was a valid platform for research into FEP. Nevertheless, the plausibility of our statistically-guided approach depends on the extent to which: (1) symptom dimensions represent coherent environmental and biological factors; and (2) meaningful clinical information or decisions may derive from the latent constructs.

From a research perspective, our findings suggest that the general dimension may reflect a phenotype for the study of general risk factors. For example, urbanicity may impact on the risk and profile of psychosis through the combination of other, more specific socio- or bio-environmental factors. In addition, we showed a substantial variation of sociodemographic determinants at the specific dimension level, which may support an integrated socio-developmental model of psychosis (Morgan *et al.*, 2010).

We may further suggest using the general dimension as a quantitative measure of psychopathology for research into the genetic component shared across psychotic disorders. The evidence is required to establish the extent to which pathophysiology of schizophrenia, bipolar disorder, and psychotic depression is shared at the level of pathways and neuronal cell mechanisms (Forstner *et al.*, 2017). Based on the data presented on specific symptom dimensions, it is intriguing to speculate whether the distribution of psychotic symptoms reflects a gradient of neurodevelopmental impairment or socio-environmental risk (Morgan *et al.*, 2010; Howes and Murray, 2014) resulting in different patterns of functional abnormalities (Murray and Lewis, 1987; Murray *et al.*, 1992; Demjaha *et al.*, 2011; Owen and O'Donovan, 2017).

From a clinical perspective, although each patient presents with a specific pattern of psychopathology and response to treatment at FEP, attention has been traditionally focused on the positive dimension management. Mental health professionals may integrate observations of the whole range of symptoms and signs with a consideration of neurodevelopmental and socio-environmental risk factors. Such an approach should aim to plan and optimize pharmacological and non-pharmacological treatments (Murray *et al.*, 2016), thus focusing further on treatment of negative, disorganized and affective dimensions (Wykes *et al.*, 2011; Giacco *et al.*, 2012; Carbon and Correll, 2014; Pelayo-Teran *et al.*, 2014; Rosenbaum *et al.*, 2014).

We may further suggest promoting mental health professionals to adopt treatment plans guided by dimensions, and increasing their confidence in dimensional classifications. Reconciling contradictory concerns of clinicians and researchers (Kendell and Jablensky, 2003) may represent the first milestone towards a gradual nosology refinement.

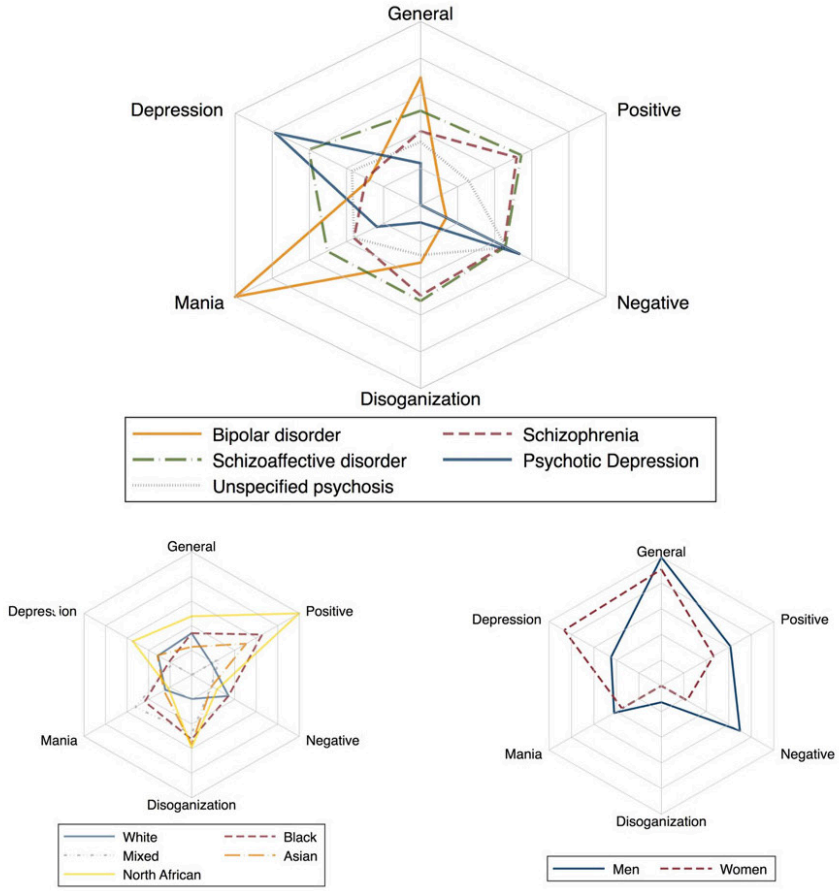

Fig. 2. Predicted symptom profiles by RDC-based diagnostic category, gender, and ethnicity. Explanatory note: After the estimation of the bifactor model, the continuous scores for general and specific symptom dimensions were computed using the function 'FSCORES' in *Mplus* (setting mean = 0 and standard deviation = 1), and used as the outcome variable in the regression analyses.

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4.2 Study 1, supplementary material

Supplementary Table S1
Prevalence of non-affective and affective psychotic symptoms in the analysed sample

OPCRIT ITEM	Item no.	Factor	Valid frequency Total sample	Valid frequency Face-to-face assessment	Valid frequency Case note review
Persecutory Delusions	54	POS	71.1% (1,551)	71.6% (794)	71% (757)
Well organised delusions	55	POS	35.1% (765)	41.6% (458)	28.8% (307)
Delusions of influence	58	POS	33.3% (726)	24.1% (267)	15.4% (165)
Bizarre Delusions	59	POS	30.7% (669)	23.3% (259)	11.3% (121)
Widespread Delusions	60	POS	34.4% (751)	42.4% (437)	29.6% (314)
Delusions of passivity	61	POS	12.2% (264)	15.2% (168)	9% (96)
Primary delusional perception	62	POS	20.5% (440)	26.2% (286)	14.6% (154)
Other primary delusions	63	POS	17% (370)	19.4% (213)	14.9% (157)
Delusions & hallucinations last for one week	64	POS	51.4% (1076)	47.9% (495)	54.8% (581)
Persecutory delusions & hallucinations	65	POS	28.1% (591)	30.1% (311)	26.2% (280)
Thought insertion	66	POS	11.2% (241)	16.4% (180)	5.8% (61)
Thought broadcast	68	POS	10.2% (221)	15.5% (171)	4.7% (50)
Third person auditory hallucinations	73	POS	24.5% (531)	29.3% (322)	19.7% (209)
Running commentary voices	74	POS	19.5% (422)	24.1% (266)	14.7% (156)
Abusive/accusatory/persecutory voices	75	POS	35% (732)	31.8% (329)	38.1% (403)
Other (non-affective) auditory hallucinations	76	POS	20.6% (446)	23.3% (264)	17.2% (182)
Non-affective hallucination in any modality	77	POS	24.8% (537)	26.7% (294)	23% (243)
Negative formal thought disorder	29	NEG	17.5% (378)	19% (209)	16%(169)
Restricted affect	32	NEG	31.3% (679)	36.4% (404)	25.9% (275)
Blunted affect	33	NEG	17.7% (374)	21.9% (243)	12.3% (131)
Bizarre behaviour	17	DIS	53.1% (1,147)	44.9% (496)	61.7% (651)
Speech difficult to understand	26	DIS	24% (520)	20.9% (230)	27.2% (290)
Incoherent	27	DIS	10.4% (226)	13% (13)	7.7% (82)
Positive formal thought disorder	28	DIS	25.8% (558)	24.3% (268)	27.3% (290)
Inappropriate affect	34	DIS	16.2% (351)	19.6% (216)	12.7% (135)
Excessive activity	19	MAN	19.6% (426)	25.5% (283)	13.5% (143)
Reckless activity	20	MAN	15.2% (330)	21% (233)	9.1% (97)
Distractibility	21	MAN	37% (799)	47.4% (521)	26.3% (278)
Reduced need for sleep	22	MAN	26.1% (565)	30.8% (340)	21.2% (225)
Agitated activity	23	MAN	34.1% (740)	41.3% (457)	26.7% (283)
Pressured speech	30	MAN	20.3% (440)	23% (255)	17.4% (185)
Thoughts racing	31	MAN	21.6% (467)	33% (365)	9.7% (102)
Elevated mood	35	MAN	18.1% (395)	20.6% (229)	15.5% (166)
Irritable mood	36	MAN	39.4% (857)	47.7% (529)	30.7% (328)
Increased self esteem	56	MAN	19.8% (432)	24.1% (267)	15.4% (165)
Grandiose Delusions	57	MAN	17.4% (380)	23.3% (259)	11.3% (121)
Slowed activity	24	DEP	16.1% (349)	23.6% (261)	8.3% (88)
Loss of energy/tiredness	25	DEP	33.7% (729)	40.1% (444)	26.7% (285)
Dysphoria	37	DEP	46.4% (1,009)	48.7% (540)	44% (469)
Loss of pleasure	39	DEP	37.8% (815)	43.2% (477)	32% (338)
Poor concentration	41	DEP	49.1% (1,061)	61% (676)	36.6% (385)
Excessive self-reproach	42	DEP	19.4% (422)	25.8% (286)	12.8% (136)
Suicidal ideation	43	DEP	27.9% (606)	34.2% (380)	21.3% (226)
Initial insomnia	44	DEP	46.7% (1,005)	52.4% (576)	40.8% (429)
Middle insomnia (broken sleep)	45	DEP	33.6% (723)	38.4% (423)	28.6% (300)
Early morning waking	46	DEP	17.3% (372)	24.9% (274)	9.3% (98)
Excessive sleep	47	DEP	10.6% (228)	15.2% (168)	5.7% (60)
Poor appetite	48	DEP	34.6% (743)	37% (407)	32.1% (336)
Weight Loss	49	DEP	22.1% (469)	29.3% (315)	14.8% (154)

Supplementary Tables S2.1 and S2.2

Model fit statistics of unidimensional, multidimensional, bi-factor, and second-order models for different assessment methods

Supplementary Table S2.1

Item ratings based on face-to-face interview[a]

Sample size: 1,112				
	Full information fit statistics[b]			
	LL	AIC	BIC	SABIC
A - Unidimensional Model	-29965	60126	60618	60306
B - Multidimensional Model (five uncorrelated factors)	-28070	56335	56826	56515
C - Multidimensional Model (five correlated factors)	-27894	56004	56546	56202
D - Bifactor Model (one general factor and five specific uncorrelated factors)	-27597	55489	56226	55759
E - Hierarchical Model (five first-order specific correlated factors and one second order general factor)	-27995	56197	56713	56386

LL, log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SABIC Sample-size Adjusted Bayesian Information Criterion

a. Only items with a valid frequency of 'present' ≥10% were analysed

b. A difference of 10 in AIC, BIC and SABIC is considered important. Lower values indicate a statistically better model fit

Supplementary Table S2.2

Item ratings based on case note review[a]

Sample size: 1,070				
	Full information fit statistics[b]			
	LL	AIC	BIC	SABIC
A - Unidimensional Model	-23708	47595	48037	47755
B - Multidimensional Model (five uncorrelated factors)	-22239	44656	45099	44816
C - Multidimensional Model (five correlated factors)	-22159	44515	45008	44693
D - Bifactor Model (one general factor and five specific uncorrelated factors)	-21668	43594	44236	43826
E - Hierarchical Model (five first-order specific correlated factors and one second order general factor)	-22227	44640	45103	44808

LL, log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SABIC Sample-size Adjusted Bayesian Information Criterion

a. Only items with a valid frequency of 'present' ≥10% were analysed

b. A difference of 10 in AIC, BIC and SABIC is considered important. Lower values indicate a statistically better model fit

Supplementary Table S3

Correlation between OPCRIT simplified scores and latent factor scores derived from the confirmatory factor analysis[a]

Symptom dimension	r (95% CI)[b]
General	0.84 (0.82 to 0.84)
Positive	0.9 (0.89 to 0.91)
Negative	0.96 (0.96)
Disorganization	0.93 (0.92 to 0.93)
Mania	0.85 (0.84 to 0.86)
Depression	0.96 (0.96 to 0.97)

a. OPCRIT simplified scores for each symptom dimension were obtained by the sum of the item weighted by the sign of the factor loading and divided by the number of valid items in each observation
b. All p values <0.001

Supplementary Table S4
Latent factor scores by ICD-10 diagnosis[a]

	General B (95% CI)	Positive B (95% CI)	Negative B (95% CI)	Disorganization B (95% CI)	Mania B (95% CI)	Depression B (95% CI)
ICD-10 Diagnosis[a]						
Schizophrenia v. Bipolar	-0.86*** (-1 to -0.73)	0.94*** (0.78 to 1.1)	0.55*** (0.39 to 0.71)	-0.08 (-0.23 to -0.07)	-1.5*** (-1.63 to -1.36)	0.18** (0.05 to 0.31)
Schizoaffective disorder v. Bipolar	-0.3* (-0.58 to -0.07)	1.01*** (0.71 to 1.03)	0.7*** (0.39 to 1.01)	-0.4** (-0.68 to -0.11)	-1.14*** (-1.4 to -0.88)	0.91*** (0.66 to 1.17)
Major Depression v. Bipolar	-1.3*** (-1.45 to -1.13)	0.39*** (0.20 to 0.58)	0.65*** (0.46 to 0.85)	-0.45*** (-0.63 to -0.26)	-1.7*** (-1.87 to -1.53)	1.56*** (1.4 to 1.72)
Unspecified Functional Psychosis v. Bipolar	-0.92*** (-1 to -0.78)	0.37*** (0.22 to 0.53)	0.49*** (0.33 to 0.65)	-0.22** (-0.37 to -0.11)	-1.14*** -1.4 to -0.88)	0.27*** (0.14 to 0.41)

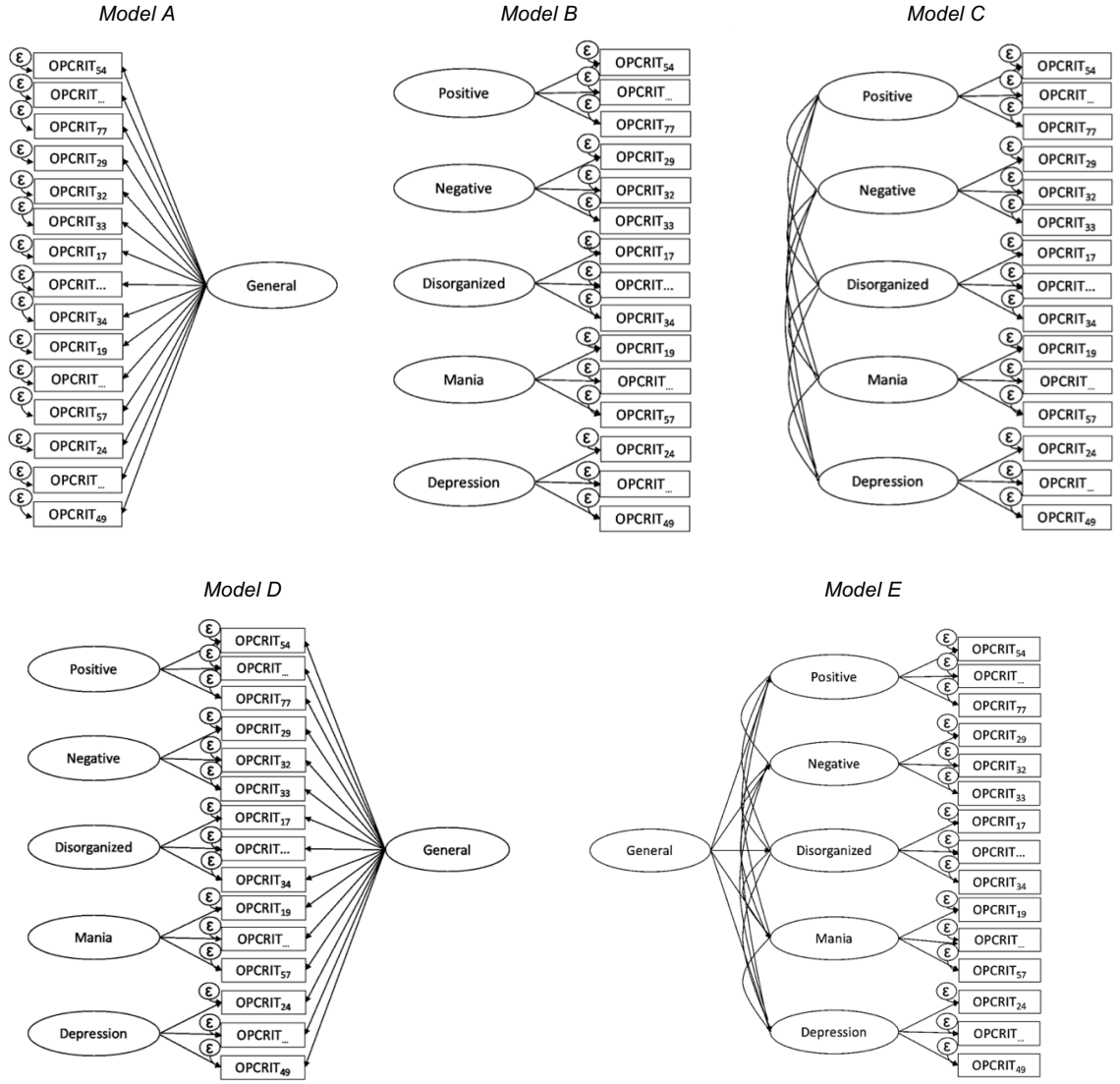
a. The analyses were controlled for gender, age, ethnicity, country, and type of assessment method (interview v. case records)

Supplementary Table S5
Latent factor scores by urbanicity within country[a,b]

	General B (95% CI)	Positive B (95% CI)	Negative B (95% CI)	Disorganization B (95% CI)	Mania B (95% CI)	Depression B (95% CI)
Site[c]						
London vs. Cambridge	0.24 (-0.02 to 0.5)	0.46** (0.11 to 0.8)	0.36* (0.08 to 0.63)	-0.2 (-0.51 to 0.1)	0.09 (-0.22 to 0.4)	0.14 (-0.13 to 0.43)
Amsterdam v. Gouda and Voorhout	0.17 (-0.17 to 0.21)	-0.12 (-0.43 to 0.18)	0.26 (-0.05 to 0.57)	0.46** (0.202 to 0.717)	0.04 (-0.26 to 0.33)	-0.1 (-0.37 to 0.17)
Palermo v. Verona, Bologna	0.06 (-0.11 to 0.24)	0.04 (-0.14 to 0.23)	0.06 (-0.15 to 0.28)	0.09 (-0.09 to 0.27)	-0.03 (-0.2 to 0.13)	-0.17* (-0.32 to -0.02)
20th arrondissement of Paris, Paris (Val-de-Marne) v. Puy-de-Dôme	-0.24 (-0.79 to 0.32)	0.08 (-0.74 to 0.57)	0.03 (-0.66 to 0.59)	0.6 (-0.11 to 1.32)	0.44 (-0.14 to 1)	-0.25 (-0.81 to 0.29)
Barcelona, Valencia, Madrid(Vallecas), v. Oviedo, Santiago, Cuenca	0.62*** (0.37 to 0.88)	-0.48** (-0.77 to -0.19)	-0.38* (-0.69 to -0.07)	-0.07 (-0.32 to 0.17)	0.05 (-0.28 to 0.18)	-0.03 (-0.25 to 0.19)

a. Brazil excluded from this analysis as only a single setting was part of the EU-GEI study
b. The analyses were controlled for age, gender, ethnicity, diagnosis, and type of assessment (interview vs. case records)
c. Population density was dichotomized at its median for defining urban and less urban settings.

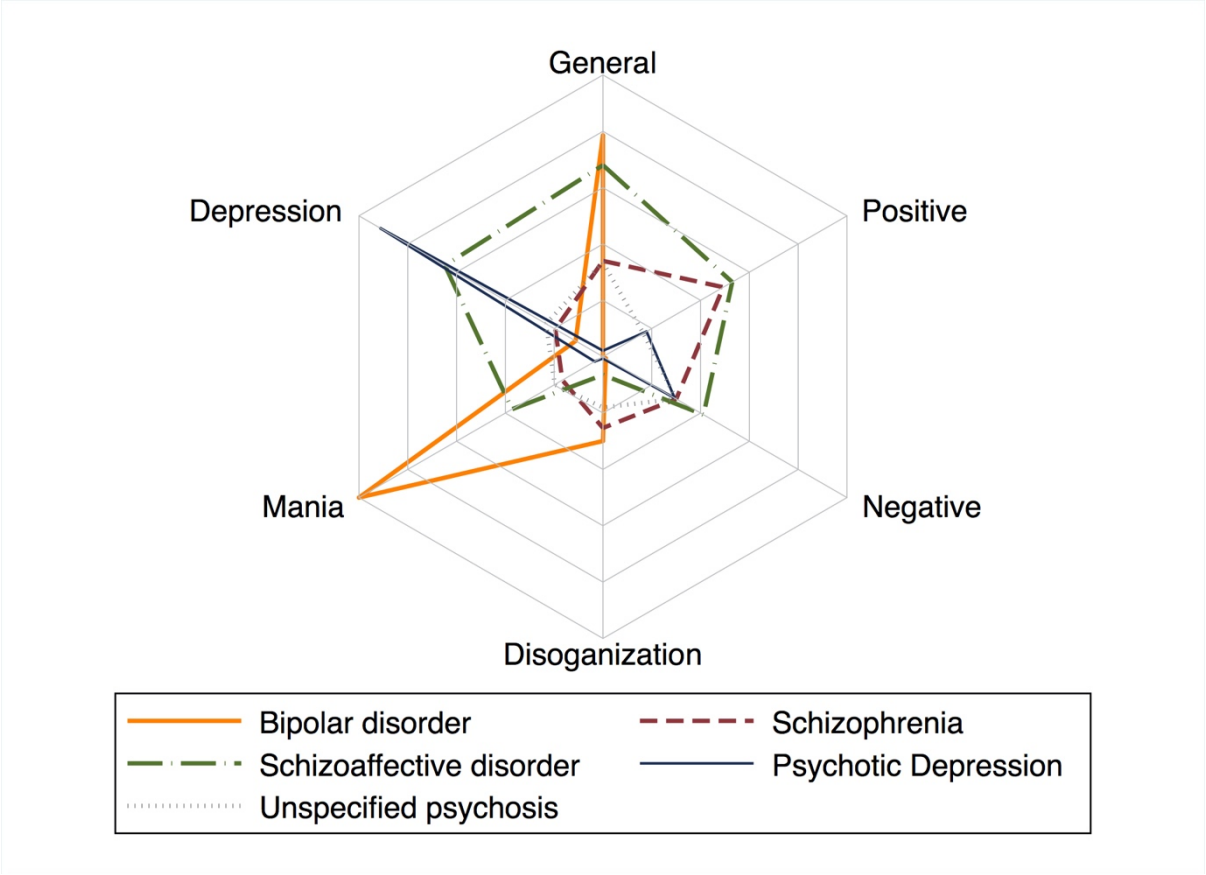
Supplementary Figure S1
Path diagrams of the five theory-based models of psychopathology[a]



(▭) Observed symptoms (OPCRIT items); (Ö) Unobserved variables (latent factors); (→) item loading on latent factors; (ε) item error variance; G, general psychosis factor; Specific symptom factors: DEP, Depression; MAN, Mania; DIS, Disorganization; NEG, Negative; POS, Positive. OPCRIT item numbers are showed in Tables S1; for simplicity, only three items for each latent factor are presented in the diagrams.

a. Explanatory note: *Model A*: unidimensional model with one unique general factor; *Model B*: multidimensional model with five uncorrelated specific factors; *Model C*: multidimensional model with five correlated specific factors; *Model D*: bifactor model with one general factor and five uncorrelated specific factors; Model *E*: hierarchical model with five correlated first-order specific factors and one general second-order factor

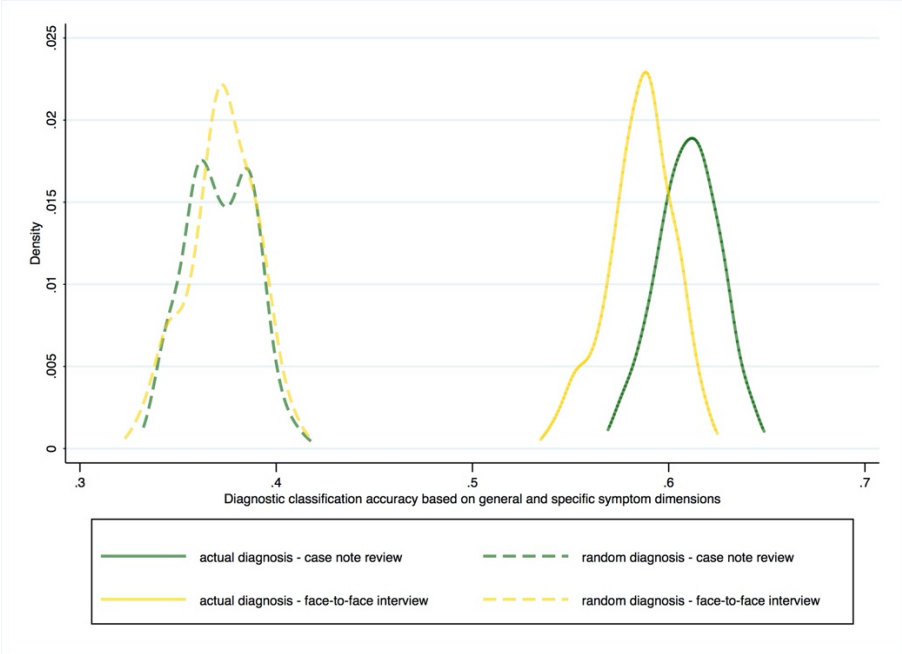
Supplementary Figure S2
Symptom profiles for general and specific symptom dimensions by ICD-based diagnostic category[a]



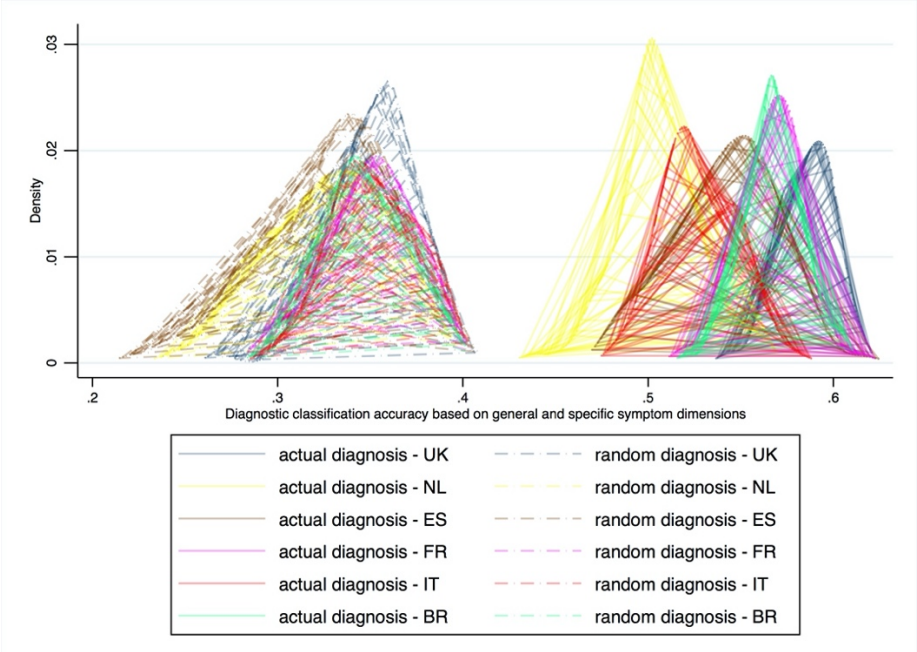
a. Explanatory note: Predicted symptom dimension scores by ICD-based diagnostic categories. The continuous symptom dimension scores were computed using the function 'FSCORES' in M*plus* (setting mean=0 and standard deviation=1), and used as the outcome variable in the model.

Supplementary Figures S3.1 and S3.2
Diagnostic classification accuracy of general and specific symptom dimensions compared with a classification by chance

Supplementary figure S3.1[a,c]



Supplementary figure S3.2[b,c]



Explanatory note 1: Figure S3.1 shows the density distribution (*y-axis*) of the subjects classified in the correct RDC diagnosis (*x-axis*) on the basis of general and specific symptom dimensions scores. Classification accuracy for subjects with psychopathology rating based on face-to-face interview (95% CI 0.54-0.63), and based on the case note review (95% CI 0.56-0.65), is compared with a classification by chance (95% 0.32-0.41).
Explanatory note 2: Figure S3.2 shows the density distribution (*y-axis*) of the subjects allocated in the correct RDC diagnosis (*x-axis*) in United Kingdom (UK), the Netherland (NL), Spain (ES), France (FR), Italy (IT), and Brazil (BR). Density peaks to the right of the plot indicates a better accuracy.

Classification of subjects based on general and specific symptom dimensions scores was more accurate than a classification by chance in all the countries.
Explanatory note 3: Multinomial ROC analysis was composed of two steps. Firstly, we ran B=100 bootstrapped multinomial regression models, predicting RDC-based diagnoses on each of the six dimension scores in a random set of patients. For each model, the quota of the subjects who were correctly classified was determined and annotated. In a second step, we ran B=100 bootstrapped multinomial regression models in each random set of patients, but this time after shuffling RDC diagnoses prior to modelling (under the null hypothesis that symptom dimension scores had no prediction power). Based on kernel density estimation, we therefore obtained 1) the density distribution of the patients correctly allocated into the diagnostic categories based on general and specific symptom dimensions scores (*actual diagnosis*); and 2) the density distribution of the patients allocated into the diagnostic categories by chance (*random diagnosis*). Based on the difference of the two distributions, we may inform on the ability of general and specific symptom dimensions to correctly classify individuals into diagnostic categories.

Chapter 5: Study 2

The current paper focuses on the variation in symptom dimensions according to different patterns of cannabis use. The study aimed to examine whether use of cannabis was associated with a particular psychopathology pattern at FEP. The existence of a cannabis-associated symptom profile raises the question whether these parameters should be considered in the clinical decision-making process. Indeed, although cannabis use is the most preventable risk factor for psychosis, specific secondary prevention strategies are barely used in early intervention services. Table 2 reports the summary of aims and hypotheses for study 2.

Table 2. Summary of aims and hypothesis for study 2

Aims	Hypothesis	Grounds of the hypothesis	Analytic approach
To examine the relationship between latent factors of psychopathology at FEP and cannabis use	The extent of lifetime exposure to cannabis is associated with more positive symptomatology at FEP in a dose-response fashion	Daily cannabis use and in use of high-potency cannabis partly explain the variation of psychosis incidence across Europe (Di Forti *et al.*, 2019a). Experimental studies show that cannabis use exacerbates positive symptoms (Hindley *et al.*, 2020).	Linear mixed models in STATA14
	Negative symptoms are more common in those who never tried cannabis	Psychosis associated with cannabis use is characterised by a less degree of neurodevelopmental impairment (Cannon *et al.*, 2002a, Murray *et al.*, 2017b)	

To identify latent factors of psychosis in the general population	A bifactor solution accounts for the variance-covariance among symptoms of psychotic experiences better than alternative solutions	Population studies showing a continuous distribution of subclinical psychotic symptoms in the general population (van Os *et al.*, 2009)	Multi-dimensional item response modelling in M*plus*
To examine the relationship between latent factors of psychosis in the general population and cannabis use	Positive psychotic experiences in population-based controls are associated with current cannabis use but not with the lifetime extent of cannabis use	Cannabis use has short-term psychotropic effects in the majority of people (Hindley *et al.*, 2020)	Linear mixed models in STATA14

5.1 Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: the EU-GEI case–control study

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Abstract

Background: Daily use of high potency cannabis has been reported to carry a high risk for psychotic disorder. However, the evidence is mixed on whether any pattern of cannabis use is associated with a particular symptomatology in first episode psychosis (FEP) patients.

Method: We analysed data from 901 patients and 1235 controls recruited across six countries, as part of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study. We used item response modelling to estimate two bifactor models, which included general and specific dimensions of psychotic symptoms in patients and psychotic experiences in controls. The associations between these dimensions and cannabis use were evaluated using linear mixed effects models analyses.

Results: In patients, there was a linear relationship between the positive symptom dimension and the extent of lifetime exposure to cannabis, with daily users of high potency cannabis having the highest score (B=0.35; 95%CI 0.14 to 0.56). Moreover, negative symptoms were more common among patients who never used cannabis compared with those with any pattern of use (B=-0.22; 95%CI -0.37 to -0.07). In controls, psychotic experiences were associated with current use of cannabis but not with the extent of lifetime use. Neither patients nor controls presented differences in depressive dimension related to cannabis use.

Conclusions: Our findings provide the first large scale evidence that first episode psychotic patients with a history of daily use of high potency cannabis present with more positive and less negative symptoms than those who never used cannabis or used low potency types.

Keywords
Cannabis use; symptom dimensions; psychopathology; psychotic experiences; cannabis-associated psychosis

Introduction

There is compelling evidence suggesting that cannabis use is associated with psychotic disorders (Marconi *et al.*, 2016). However, it is unclear whether cannabis use is a 'modifier' factor for psychotic disorders, which affects symptom presentation. The existence of a pattern of psychotic symptomatology particularly associated with cannabis has been described in several case series (Walter Bromberg, 1934, Talbott and Teague, 1969, Spencer, 1971, Bernhardson and Gunne, 1972, Chopra and Smith, 1974). Nevertheless, case and cohort studies have found mixed results as to whether (Negrete *et al.*, 1986, Peralta and Cuesta, 1992, Bersani *et al.*, 2002, Green *et al.*, 2004, Grech *et al.*, 2005, Addington and Addington, 2007, Foti *et al.*, 2010, Ringen *et al.*, 2016, Seddon *et al.*, 2016) or not (Thornicroft *et al.*, 1992, Stirling *et al.*, 2005, Dubertret *et al.*, 2006, Boydell *et al.*, 2007, van Dijk *et al.*, 2012, Tosato *et al.*, 2013, Barrowclough *et al.*, 2015) psychotic patients using cannabis present with more positive symptoms than those not using cannabis. Moreover, there is mixed evidence of any relationship between cannabis use and negative symptoms in psychosis. Some reports suggest fewer negative symptoms in psychotic patients that use cannabis (Peralta and Cuesta, 1992, Bersani *et al.*, 2002, Green *et al.*, 2004), which is consistent with having enough social skills to obtain the substance (Murray *et al.*, 2017). However, this association has not been confirmed in other studies (Grech *et al.*, 2005, Seddon *et al.*, 2016) and others even reported a positive association (Ringen *et al.*, 2016).

These inconsistencies might be explained by differences in study design and methods. For example, only a few findings were based on first episode psychosis (FEP) patients (Grech *et al.*, 2005, Addington and Addington, 2007, Tosato *et al.*, 2013, Seddon *et al.*, 2016), which minimize selection and recall bias, and the confounding effect of

antipsychotic drugs on symptoms. In addition, a metanalysis of longitudinal studies concluded that most results lacked sufficient power to detect an effect of cannabis on symptoms, or inadequately controlled for potential confounders (Zammit *et al.*, 2008). Furthermore, although a few studies included information on frequency of use, all failed to obtain detailed information on the lifetime pattern of cannabis use, especially on the type and strength of cannabis used. Of note, potent cannabis varieties, with high concentrations of Delta-9-Tetrahydrocannabinol (Δ9-THC), have been associated with the most harm to mental health (Di Forti *et al.*, 2015, Freeman *et al.*, 2018) and, in recent years, these potent types have become more available worldwide (ElSohly *et al.*, 2016, Potter *et al.*, 2018, Freeman *et al.*, 2019). Finally, no studies have used factor analysis of observed symptoms to evaluate to what extent cannabis use is a factor influencing the clinical heterogeneity of psychosis.

On the other hand, in the general population there are consistent findings regarding the association between cannabis use and psychotic experiences (Ragazzi *et al.*, 2018). However, most studies had limited geographical coverage and the examined population was scarcely representative of the population at risk of psychosis (Ragazzi *et al.*, 2018).

In this study, we set out to clarify the association between detailed patterns of cannabis use and transdiagnostic symptom dimensions in a large multinational FEP sample. In addition, we examine the association between detailed patterns of cannabis use and subclinical symptom dimensions in a large sample of controls representative of the population at risk in each catchment area.

Specifically, we sought to test the hypotheses that: (1) positive psychotic symptoms are more common among FEP patients with more frequent lifetime use of cannabis and greater exposure to use of high potency varieties; (2) positive psychotic

experiences are more common in population controls with a recent use of cannabis, who would be more resilient to the long-term effects of cannabis; (3) negative symptoms are more common among those patients who have never used cannabis.

Methods

Study design and participants

This analysis is based on the incidence and case-control study work package of the EUropean network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI).

FEP individuals were identified between 2010 and 2015 across six countries to examine incidence rates of schizophrenia and other psychotic disorders (Jongsma *et al.*, 2018), and symptomatology at psychosis onset (Quattrone *et al.*, 2019). For examining risk factors, we sought to perform an extensive assessment on approximately 1,000 FEP patients and 1,000 population-based controls during the same time period.

Patients were included in the case-control study if they met the following criteria during the recruitment period: (a) aged between 18 and 64 years; (b) presentation with a clinical diagnosis for an untreated FEP, even if longstanding [International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes F20-F33]; (c) resident within the catchment area. Exclusion criteria were: (a) previous contact with psychiatric services for psychosis; (b) psychotic symptoms originating from an identified organic condition; and (c) transient psychotic symptoms resulting from acute intoxication (ICD-10: F1x.5).

The recruitment of controls followed a mixture of random and quota sampling methods, in order to achieve the best possible representativeness in age, sex, and ethnicity of

the population living in each catchment area. The identification process varied by site and was based on locally available sampling frames, including mostly the use of lists of all postal addresses and general practitioners' lists from randomly selected surgeries. When these resources were not fully available, internet and newspapers advertising were used to fill quotas. Exclusion criteria for controls were: (a) diagnosis of a psychotic disorder; (b) ever having been treated for psychotic symptoms.

We analysed data from eleven catchment areas, including urban and less urban populations (i.e. Southeast London, Cambridgeshire and Peterborough (England); central Amsterdam, Gouda and Voorhout (the Netherlands); Bologna municipality, city of Palermo (Italy); Paris [Val-de-Marne], Puy-de-Dôme (France); Madrid [Vallecas], Barcelona (Spain); and Ribeirão Preto (Brazil). Further information on the case-control sample and the recruitment strategies is included in the supplementary material.

Measures

Data on age, sex, and ethnicity were collected using a modified version of the Medical Research Council Sociodemographic Schedule (Mallett, 1997). The OPerational CRITeria (OPCRIT) system (McGuffin *et al.*, 1991) was used by centrally trained investigators, whose reliability was assessed before and throughout the study (k=0.7), to assess psychopathology in the first four weeks after the onset and generate research-based diagnoses based on different diagnostic classification systems. The Community Assessment of Psychic Experiences (CAPE) (Stefanis *et al.*, 2002) was administered to controls to self-report their psychotic experiences. The reliability of the CAPE is good for all the languages spoken in the countries forming part of the EU-GEI study (http://cape42.homestead.com).

A modified version of the Cannabis Experience Questionnaire ($CEQ_{EU\text{-}GEI}$) (Di Forti *et al.*, 2009) was used by investigators to collect extensive information on the patterns of

use of cannabis and other drugs. We used six measures of cannabis use (Supplementary Table S2), including a variable measuring specific patterns of cannabis exposure by combining the frequency of use with the potency of cannabis. As illustrated in the supplementary material, the cannabis potency variable was based on the data published in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (European Monitoring Centre for Drugs and Drug Addiction, 2013, Di Forti *et al.*, 2019).

We selected confounders based on their possible association with cannabis use and/or symptom dimensions. These included: sex; age; ethnicity; use of stimulants, hallucinogens, ketamine, cocaine, crack, and novel psychoactive substances; current use of cigarettes (smoking 10 cigarettes or more per day=1), and current use of alcohol (drinking 10 alcohol units or more per week=1).

Statistical analysis

Dimensions of psychotic symptoms in patients and psychotic experiences in controls

Data from OPCRIT and CAPE were analysed using multidimensional item response modelling in M*plus*, version 7.4 (Muthén and Muthén, 2012), to estimate two bifactor models, based on the associations among observer ratings of psychotic symptoms in patients and self-ratings of psychotic experiences in controls. This methodology is described in full in our EU-GEI paper on symptom dimensions in FEP patients (Quattrone *et al.*, 2019), and it was likewise applied to psychotic experiences in population controls. Briefly, CAPE items were dichotomized as 0 ‘absent’ or 1 ‘present’. In order to ensure sufficient covariance coverage for item response modelling, we used items with a valid frequency of ‘present’ ≥10% in our sample, and we excluded items with low correlation values (<.3) based on the examination of the

item correlation matrix. As in the previous analysis in patients, the bifactor solution was compared with other solutions (i.e., unidimensional, multidimensional, and hierarchical models) using Log-Likelihood (LL), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Sample-size Adjusted BIC (SABIC) as model fit statistics. Path diagrams that illustrate these models are presented in Supplementary Figure S1. Reliability and strength indices such as McDonald's omega (ω) (Rodriguez *et al.*, 2016), omega hierarchical (ω_H) (Rodriguez *et al.*, 2016), and index *H* (Hancock and Mueller, 2001), were computed to determine: 1) the proportion of common variance accounted by general and specific symptom dimensions; 2) the proportion of reliable variance accounted by the general dimension not unduly affected by the specific dimensions; 3) the proportion of reliable variance accounted for by each specific dimension not unduly affected by the general and all the other specific dimensions; 4) the overall reliability and replicability of the bifactor construct of psychosis-like experiences. Finally, we generated factor scores for one general psychotic experience dimension and three specific dimensions of positive, negative, and depressive psychotic experiences.

For patients, we used the previously generated factor scores for one general psychosis dimension and five specific dimensions of positive, negative, disorganised, manic, and depressive symptoms (Quattrone *et al.*, 2019).

Symptom dimensions and cannabis use

We evaluated the relationship between psychotic symptom dimensions in patients, or psychotic experience dimensions in controls, and cannabis use using linear mixed effects models in STATA14 (StataCorp, 2015). We specifically modelled symptom dimension scores as a function of each of the six measures of cannabis use. We then evaluated the combined effect of frequency of use and potency of cannabis. To

account for the non-independence of symptom profiles of subjects assessed within the same country (for example, due to cultural similarities), and for the potential within-site correlation (for example, due to context factors), we fitted a three-level mixed model, where the random effect encompassed two levels of random intercepts: one due to the countries, and another due to the sites within the countries. Finally, we used the Benjamini-Hochberg (B-H) procedure to reduce the false discovery rate, which we set at 5%.

Results

Sample characteristics

We analysed data from 901 FEP patients and 1,235 controls. The main socio-demographic characteristics and history of substance misuse of patients and controls are presented in Supplementary Table S1. Supplementary Tables S3 and S5 show the sample prevalence of psychotic experiences in controls and of psychotic symptoms in patients.

Bifactor model of psychotic experiences in controls

Supplementary Table S4 shows that, as in our previous analysis of the OPCRIT items (Quattrone *et al.*, 2019), the bifactor model provided the best fit for the CAPE items, as illustrated by AIC, BIC and SABIC substantially lower compared with competing models. This solution explained 60% of the unique variance. In addition, Figure 1 shows that, within the bifactor model, the explained variance was due to individual differences mostly on the general psychotic experience dimension. This is illustrated by the relative omega coefficient, which, for example, showed that 85% of the reliable variance was due to the general dimension when partitioning out the variability in scores due to the specific dimensions. Moreover, factor loadings of moderate to high

magnitude were observed for most items on the general psychotic experience dimension, whereas factor loadings of a smaller magnitude were observed for the specific dimensions (Figure 1). Consistently, the index *H*, which is a measure of the construct reliability and replicability across studies (Hancock and Mueller, 2001), was very high for the general dimension (0.92), moderate for positive (0.78) and negative (0.71) dimensions and lower for the depressive dimension (0.41).

Symptom dimensions in patients by pattern of cannabis use

Models' results are presented in Table 1.1 which shows that:

1) There were no differences in the distribution of positive symptoms according to early age at first use (=<15 years old), nor, after B-H correction, according to ever or current use of cannabis. However, positive symptoms were more common among patients who spent more than 20 euros per week on cannabis (B=0.3; 95%CI 0.11 to 0.48; p=0.001).

2) Fewer negative symptoms were observed among those patients who used cannabis at least once compared with those who never tried (B=-0.22; 95%CI -0.37 to -0.07; p=0.004). Early age at first use and current use of cannabis was not associated with negative symptomatology.

3) Manic symptoms were more frequent among patients who had ever used cannabis (B=0.22; 95%CI 0.08 to 0.36; p=0.002).

4) There were no differences in the distribution of the scores on the depressive, disorganization and general psychosis dimensions according to any measure of cannabis use.

Psychotic experience dimensions in population controls by patterns of cannabis use

Models' results are presented in Table 1.2, which shows that:

1) There were no differences in the distribution of positive psychotic experiences according to ever use of cannabis or early age at first use (=<15 years old). However, positive psychotic experiences were more commonly reported by subjects who currently used cannabis (B=0.33; 95%CI 0.15 to 0.51; p<0.001) and who spent more than 20 euros per week on cannabis (B=0.39; 95%CI 0.09 to 0.69; p=0.011).

2) There were no differences in the distribution of the depressive and negative experiences in population controls according to cannabis use.

Symptom dimensions by frequency of use and potency of cannabis

The independent effects of frequency of use and potency of cannabis is reported in Supplementary Tables S6.1 and S6.2, and Supplementary Figure S2, showing that, only in patients, positive symptoms were more common in those who used cannabis on a daily basis and exposed to high potency varieties

Testing the combined 'type-frequency' variable in patients, we found evidence of a linear relationship between the positive symptom dimension and the extent of exposure to cannabis, with daily users of high potency cannabis showing the highest score (B=0.35; 95%CI 0.14 to 0.56; p=0.001). Therefore, we introduced a contrast operator and plotted the exposure-response relationship for positive symptoms (Figure 2), by comparing the predictive margins of the adjusted mean of each group against the grand adjusted mean of all groups. Figure 2 shows that the adjusted mean for daily users of high potency cannabis was 0.2 units greater than the grand adjusted mean. Moreover, the adjusted means for the groups who never or rarely used cannabis were respectively 0.16 or 0.18 units lower than the grand adjusted mean.

A negative relationship between the negative symptom dimension score and patterns of cannabis use was also observed in patients. Figure 3 shows that patients with psychosis who never used cannabis had more negative symptoms either compared with the grand adjusted mean or with any pattern of cannabis use.

Discussion

Principal findings

This is the first multinational study analysing data on the potency of the cannabis used by FEP patients to investigate a dose effect relationship between cannabis use and dimensions of symptoms, and also its effect on dimensions of psychotic experiences in population controls. We provide the first evidence that: 1) in patients, a positive correlation exists between the extent of premorbid cannabis use and the score on the positive symptom dimension, with daily users of high potency cannabis showing the most positive symptoms at FEP; 2) psychotic experiences in non-clinical populations are associated with current use of cannabis but are independent of the extent of lifetime exposure to cannabis; 3) negative symptoms at FEP are more common in patients who have never tried cannabis; 4) depressive symptoms are independent of any pattern of use of cannabis.

Limitations

Our findings must be considered in the context of two main limitations. First, individual data on patterns of cannabis use are not validated with biological samples. However, biological tests are not considered the gold standard method for such a validation (Large *et al.*, 2012) and would not allow one to ascertain the extent of cannabis use over the years (Taylor *et al.*, 2017). Moreover, studies combining self-report and laboratory data support the reliability of subjects in reporting the type of cannabis they use (Wolford *et al.*, 1999, Freeman *et al.*, 2014). Second, we did not take into account

the cannabidiol (CBD) contribution to the potency variable, as official data on its content in the different cannabis varieties were not available in most study sites; CBD might counterbalance Δ9-THC effects and minimise both psychotic experiences (Schubart *et al.*, 2011) and symptoms (McGuire *et al.*, 2018).

Comparison with previous research

We extend previous research on cannabis and psychotic symptoms to a multinational sample confirming the association between cannabis use and positive symptoms of FEP (Ringen *et al.*, 2016, Seddon *et al.*, 2016). Our results are in line with Schoeler et al. (2016), who carefully scrutinised the literature on the effect of continuation of cannabis use after FEP, concluding that this would be associated with a more severe positive symptomatology (Schoeler *et al.*, 2016). That said, any comparison with previous research is limited by the lack of information on frequency and potency in all the previous studies along with subjects' exposure to more potent varieties of cannabis in recent years (Potter *et al.*, 2018). In this respect, we firstly provide some evidence that cannabis affects positive symptoms in a dose response manner, further supporting the converging epidemiological and experimental evidence that the use of cannabis with high content of Δ9-THC has a more detrimental effect than other varieties (Di Forti *et al.*, 2009, Morrison *et al.*, 2009, Freeman *et al.*, 2018).

We also report evidence in a multinational FEP sample of an association between lifetime cannabis use and fewer negative symptoms, the latter often considered as a marker of greater neurodevelopmental impairment in psychotic subjects. Two opposite interpretations should be discussed.

First, some authors have suggested that people with a psychotic disorder might use cannabis as an attempt to self-medicate negative symptoms, and thus the observed

reduction in negative symptomatology would be an epiphenomenon due to the cannabis intake itself (Peralta and Cuesta, 1992).

Second, psychotic disorders may be characterized by less neurodevelopmental features when associated with cannabis use (Ruiz-Veguilla *et al.*, 2012, Ferraro *et al.*, 2013, Murray *et al.*, 2017, Ferraro *et al.*, 2019), hence FEP patients who do not initiate to use cannabis would have more negative symptoms.

The lack of a dose dependency in our study appears to speak against the first and in favour of the second possibility, as the difference holds between those who never obtained cannabis and those who may have used it only once. Moreover, negative symptoms would reduce the social and instrumental skills that were necessary to obtain illegally cannabis and sustain its use in all the countries included in the study, except Holland.

Last, we report that the cumulative exposure to cannabis does not impact on psychotic experiences in controls. One could of course argue that the largest proportion of subjects with the harmful pattern of cannabis use were patients. However, further research is needed to look into plausible mechanisms of resilience to the psychotogenic effect of cannabis as observed in our controls, who report psychotic experiences if current users but do not seem to accumulate a risk over life time cannabis use and develop psychotic disorders. Indeed, future studies should aim to: 1) investigate if and how genetic factors, plausibly regulating the endocannabinoid and dopamine systems, pose a small subset of cannabis users at high risk of developing a psychotic disorders with particular symptomatology; 2) clarify over the course of the disorder whether or not differences in symptomatology between current and former cannabis users may be related to residual cannabis effects.

Implications

The novelty of our study is based on our examination of data on lifetime frequency of cannabis use and on the type of the cannabis used; high potency types are increasing worldwide. For instance, a recent potency study revealed that in London, the high potency type of cannabis called skunk has now taken up 96% of the street market (Potter *et al.*, 2018). The EMCDDA has described a European cannabis market characterised by potent varieties (European Monitoring Centre for Drugs and Drug Addiction, 2013) like those present in Amsterdam coffee shops that can reach up to 39% of THC. Indeed, as daily use, and use of high potency cannabis, have been associated both with greatest risk to develop psychotic disorders and to high rates of psychotic disorders across Europe (Di Forti *et al.*, 2019), here we show that in FEP patients daily use of high potency cannabis drives a high score on the positive symptom dimension. Further research should aim to determine biological mechanisms underlying how cannabis impacts on different clinical manifestations of psychosis. Meanwhile, translating current findings into clinical practice, symptom dimension scores can be used to stratify patients and develop secondary prevention schemes for cannabis-associated psychosis.

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Conflicts of interest
None.

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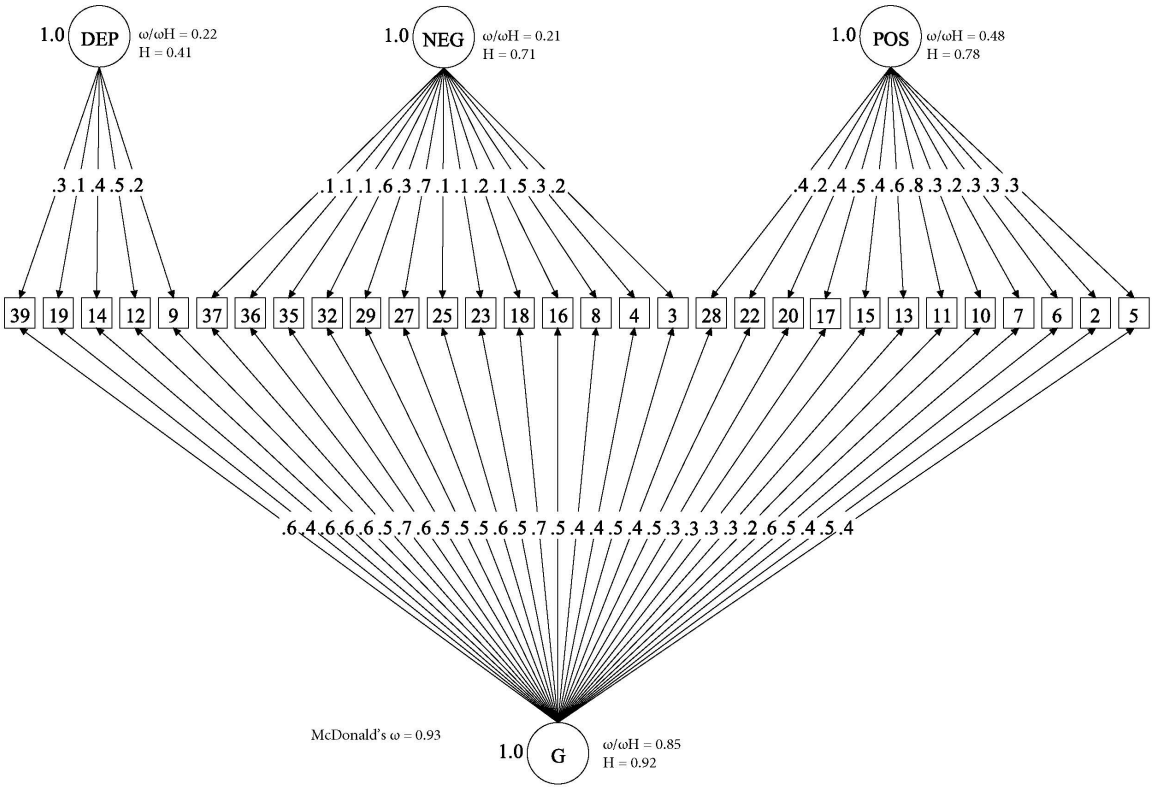
Figure 1. Bifactor model of psychotic experiences in controls



(□) Observed variables (No. of CAPE items); (○) Unobserved variables (latent factors); (→) standardized item loading estimation onto latent factors; G, general psychosis-like factor; Specific psychotic experiences factors: DEP, Depression; NEG, Negative; POS, Positive. Reliability and strenght estimates: H=construct reliability index; ω= McDonald omega; ω_H=hierarchical omega; ω/ω_H= Relative omega.
Explanatory note: McDonald's ω is an estimate of the proportion of the common variance accounted by general and specific symptom dimensions.(Rodriguez *et al.*, 2016). Relative omega (ω/ω_h) is the amount of reliable variance explained in the observed scores attributable to a) the general factor independently from the specific symptom dimensions, and 2) each specific symptom dimension independently from the general factor.
H is an index of the quality of the measurement model based on the set of CAPE items for each dimension.(Hancock and Mueller, 2001) Indices can range from 0 to 1, with values closer to 1 indicating a better construct reliability and replicability across studies.

Figure 2. Positive symptom dimension in cases by patterns of cannabis use.

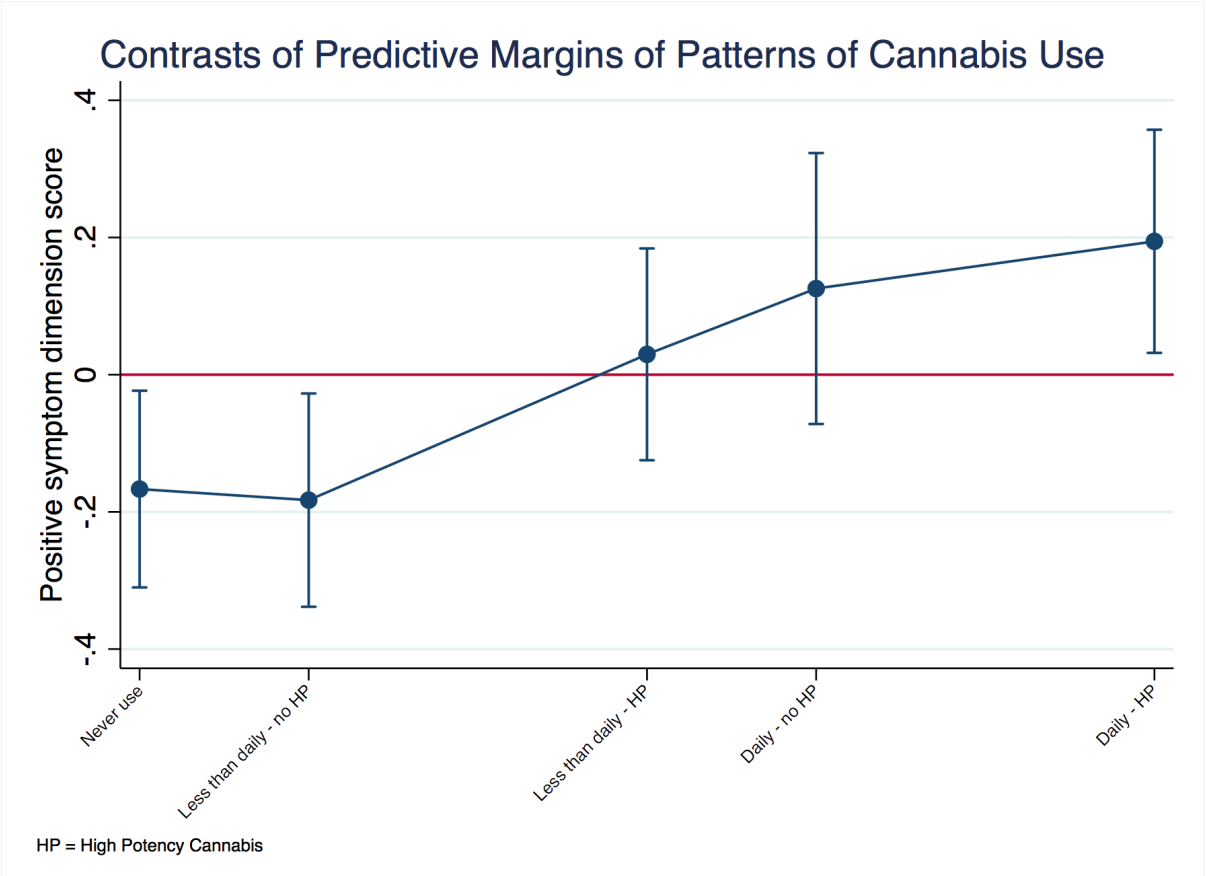


Figure 2 shows the contrasts of the positive symptom dimension predicted mean of each group of patterns of use of cannabis against the predicted grand mean of all groups (represented by the red line). The positive value for the contrast of the daily use of high potency cannabis indicates more positive symptomatology in this group. On the other hand, negative values for the contrasts of the first two groups indicates less positive symptomatology when there is less exposure to cannabis. These differences are statistically significant, as indicated by 95% confidence intervals that do not overlap with zero. The model was a random intercept model which allowed symptoms to vary across countries and sites within countries, but it assumed that frequency of use and type of cannabis had an individual fixed effect. Values were adjusted for age, sex, ethnicity, diagnosis, and use of other recreational/illicit substances.

Figure 3. Negative symptom dimension in cases by patterns of cannabis use.

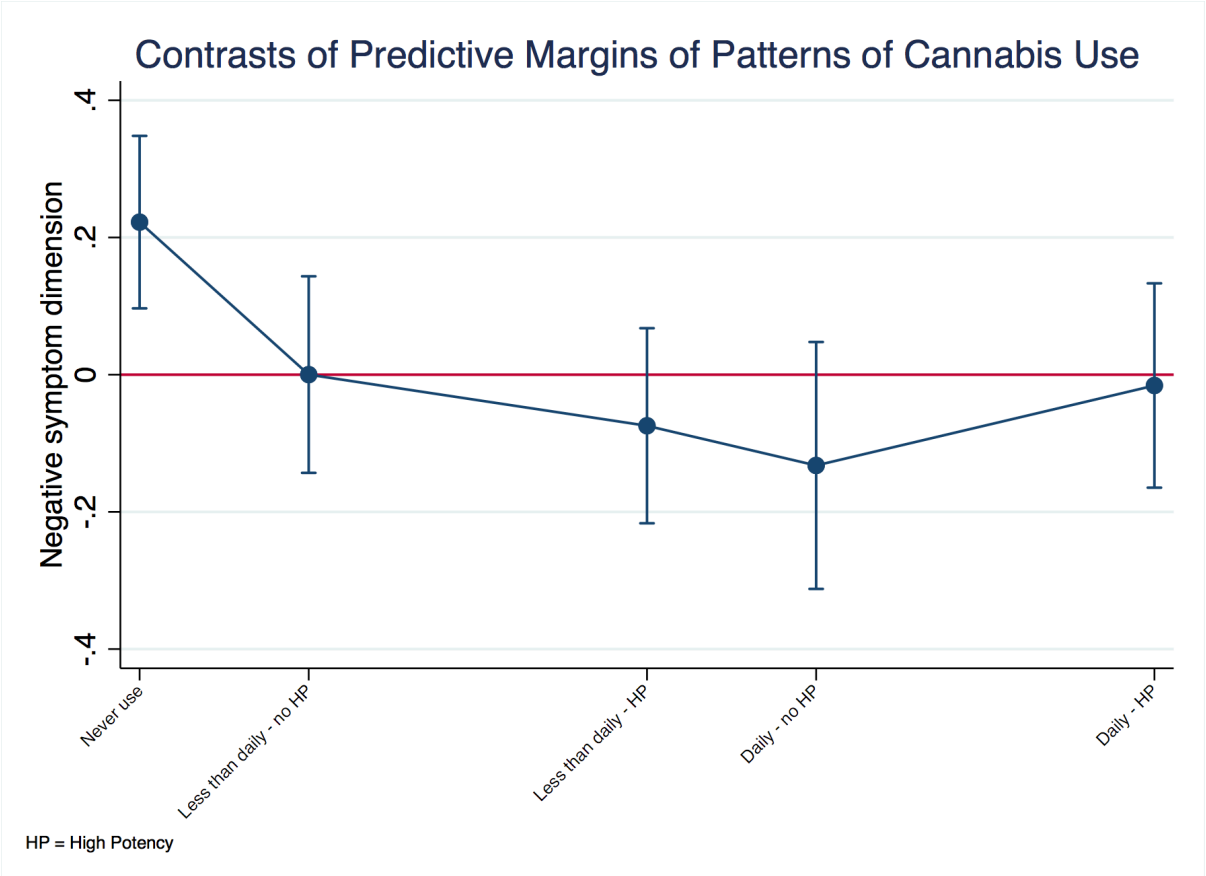


Figure 3 shows the contrasts of the negative symptom dimension predicted mean of each group of patterns of use of cannabis against the grand adjusted predicted mean (represented by the red line). Subjects who had never used cannabis presented with more negative symptoms compared to the whole sample. The model was a random intercept model which allowed symptoms to vary across countries and sites within countries, but it assumed that frequency of use and type of cannabis had an individual fixed effect.

Table 1.1 Symptom dimensions in FEP patients by measures of cannabis use[a]

Symptom dimension	Ever used cannabis B (95% CI)	Current use of cannabis B (95% CI)	Age at first use of cannabis B (95% CI)	Money used for cannabis B (95% CI)
Positive	0.16* (0 to 0.31)	0.21* (0.04 to 0.37)	0.05 (-0.13 to 0.22)	**0.3**** (0.11 to 0.48)
Negative	**-0.22**** (-0.37 to -0.07)	-0.09 (-0.26 to 0.07)	0.07 (-0.09 to 0.22)	0.07 (-0.12 to 0.25)
Depressive	-0.08 (-0.24 to 0.08)	-0.08 (-0.22 to 0.06)	-0.09 (-0.23 to 0.05)	-0.11 (-0.29 to 0.06)
Disorganization	-0.01 (-0.24 to 0.03)	0.01 (-0.05 to 0.26)	0.11 (-0.06 to 0.28)	0.1 (-0.17 to 0.19)
Manic	**0.22**** (0.08 to 0.36)	0.12 (-0.02 to 0.27)	-0.09 (-0.25 to 0.07)	0.05 (-0.11 to 0.22)
General factor	0.05 (-0.06 to 0.17)	0.02 (-0.1 to 0.14)	-0.06 (-0.09 to 0.22)	0.03 (-0.11 to 0.17)

[a]All models were adjusted for age, sex, ethnicity, use of other recreational/illicit substances, and diagnosis. Models were random-intercept models that included two random effects to allow symptomatology to vary across countries and across sites within countries but assumed that individual-level exposure to cannabis had a fixed effect across the entire sample.
Significance: * p < 0.05, ** p < 0.01, *** p < 0.001; associations that survived after Benjamini-Hochberg correction are showed in bold.

Table 1.2 Psychotic experience dimensions in controls by cannabis use[a]

Psychotic experience dimension	Ever used cannabis B (95% CI)	Current use of cannabis B (95% CI)	Age at first use of cannabis B (95% CI)	Money used for cannabis B (95% CI)
Positive	0.05 (-0.06 to 0.17)	**0.33***** (0.15 to 0.51)	0.08 (-0.11 to 0.25)	**0.39*** (0.09 to 0.69)
Negative	0.11 (-0.01 to 0.24)	0.16 (-0.03 to 0.36)	-0.11 (-0.29 to 0.07)	-0.12 (-0.2 to 0.44)
Depressive	0.09 (-0.03 to 0.21)	0.01 (-0.19 to 0.20)	-0.02 (-0.21 to 0.16)	-0.02 (-0.3 to 0.35)
General factor	0.04 (-0.08 to 0.17)	0.13 (-0.07 to 0.33)	0.08 (-0.11 to 0.22)	0.15 (-0.18 to 0.48)

[a]All models were adjusted for age, sex, ethnicity, and use of other recreational/illicit substances. Models were random-intercept models that included two random effects to allow symptomatology to vary across countries and across sites within countries but assumed that individual-level exposure to cannabis had a fixed effect across the entire sample.
Significance: * p < 0.05, ** p < 0.01, *** p < 0.001; associations that survived after Benjamini-Hochberg correction are showed in bold.

5.2 Study 2, supplementary material

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Socio-demographic characteristics and history of substance misuse of the analysed sample

	FEP N=901	**Controls N=1235**
Age (mean; SD)	30.8 (10.5)	36.1 (13.3)
Sex (male %; N)	61.9 (558)	47 (581)
Self-reported Ethnicity		
White (%; N)	59.05 (532)	75.22 (929)
Black	18.65 (168)	9.55 (118)
Mixed	11.54 (104)	9.15 (113)
Asian	3.55 (32)	2.67 (33)
North African	4.66 (42)	1.86 (23)
Others	2.55 (23)	1.54 (19)
Ever used cannabis		
Yes (%; N)	64.93 (585)	46.48 (574)
Missing	1.44 (13)	1.05 (13)
Current use of cannabis		
Yes (%; N)	21.64 (195)	10.61 (131)
Missing	1.78 (16)	1.05 (13)
Age at first use of cannabis		
Never Used (%; N)	33.63 (303)	52.47 (648)
<=15 year old	27.75 (250)	13.52 (167)
16 year old and older	35.74 (322)	32.96 (407)
Missing	2.89 (26)	1.05 (13)
Money used for cannabis (weekly)		
From 0 to 20 euro	76.47 (689)	92.3 (1,140)
More than 20 euro	16.1 (145)	3.16 (39)
Missing	7.44 (67)	4.53 (56)
Lifetime frequency of use		
Never use	56.83 (512)	52.47 (648)
Less than daily	11.54 (104)	39.68 (490)
Daily	28.86 (260)	6.72 (83)
Missing	2.77 (25)	1.13 (14)
Type of cannabis		
Never used	33.63 (303)	55.57 (648)
Less than 10% THC	26.64 (240)	23.89 (295)
More than 10% THC	32.63 (294)	18.06 (223)
Missing	7.1 (64)	5.59 (69)

Current tobacco use		
>10 cigarettes x day (%; N)	28.71 (262)	10.85 (134)
Missing	3.77 (34)	1.94 (24)
Current use of other drugs		
Stimulants (%; N) Missing	8.62 (82) 1.6 (15)	4.53 (56) 1.05 (13)
Hallucinogens Missing	5.23 (49) 1.92 (18)	2.02 (25) 1.21 (15)
Ketamine Missing	2.13 (20) 1.92 (18)	1.05 (13) 1.21(15)
Novel Psychoactive Substances Missing	1.39 (13) 1.71 (16)	0.65 (8) 1.05 (13)
Crack Missing	2.67 (25) 1.6 (15)	2 (0.16) 1.05 (13)
Cocaine Missing	14.94 (140) 1.81 (17)	5.83 (72) 1.13 (14)
Current alcohol overuse		
Drinks =>10 units per week (%; N) Missing	10.88 (98) 11.4(103)	12.47 (154) 3.24(40)
Diagnosis		
Schizophrenia (%;N)	13.2 (282)	
Schizoaffective disorders	17.84 (381)	
Bipolar Disorders	2.48 (53)	
Psychotic Depression	1.92 (41)	
Unspecified Psychosis	6.74 (144)	

Supplementary table S2. Cannabis measures in the EU-GEI study

Lifetime cannabis use	0=*never used*	1=*Yes*	
Currently using cannabis	0=*no use at the time of recruitment in the study and over the previous 4 weeks*	1=Yes	
Age at first use of cannabis	0=*started at age 16 years or older*	*1=started at age 15 years or younger*	
Lifetime frequency of use	*0=never used*	*1=used less than daily*	*2=used daily*
Money spent weekly on cannabis	*0=never used or spent 20 EURO or less per week*	*1= spent more than 20 EURO per week*	
Type of cannabis used[1]	*0= never used*	*1= types with THC<10%*	*2= types with THC=>10%*

[1]*Explanatory note: The potency variable was defined by a cut off of 10% of the THC concentration expected in the different varieties of cannabis in each catchment area, based on government and national data examined by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (European Monitoring Centre for Drugs and Drug Addiction, 2013, Di Forti et al., 2019).*

Cannabis varieties classified as low potency (THC<10%) were: hash/resin from UK and Italy, imported herbal cannabis from UK, Italy, Spain and France, Brazilian marijuana and hash and the Dutch Geimporteerde Wiet.

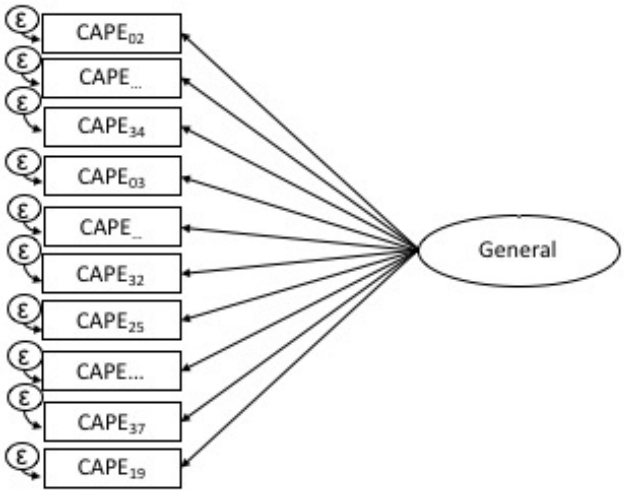
Cannabis varieties classified as high-potency (THC>10%) were: UK home-grown skunk/sensimilla UK Super Skunk, Italian home-grown skunk/sensimilla, Italian Super Skunk, the Dutch Nederwiet, Nederhasj and geimporteerde hasj, the Spanish and French Hashish (from Morocco), Spanish home-grown sensimilla, French home-grown skunk/sensimilla/super-skunk and Brazilian skunk.

Supplementary table S3. Prevalence of CAPE psychotic experiences in population controls

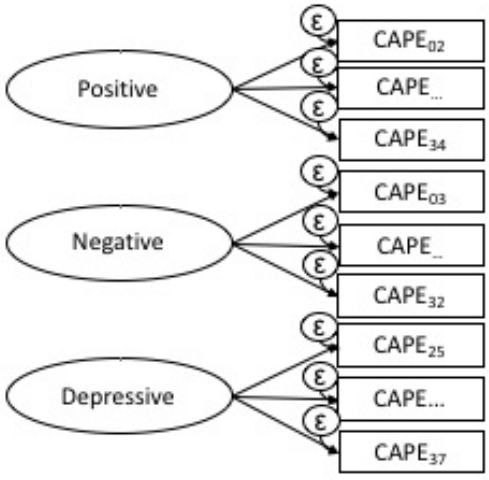
CAPE ITEM	*Item no.*	*Factor*	*Valid frequency Total sample*
Do you ever feel as if people seem to drop hints about you or say things with a double meaning?	*2*	*POS*	*50.9% (629)*
Do you ever feel as if things in magazines or on TV were written especially for you?	*5*	*POS*	*17.6% (217)*
Do you ever feel as if some people are not what they seem to be?	*6*	*POS*	*74.7% (923)*
Do you ever feel as if you are being persecuted in some way?	*7*	*POS*	*18.9% (233)*
Do you ever feel as if there is a conspiracy against you?	*10*	*POS*	*12.4% (153)*
Do you ever feel as if you are destined to be someone very important?	*11*	*POS*	*30.6% (378)*
Do you ever feel that you are a very special or unusual person?	*13*	*POS*	*35.5% (438)*
Do you ever think that people can communicate telepathically?	*15*	*POS*	*25.6% (316)*
Do you ever feel as if electrical devices such as computers can influence the way you think?	*17*	*POS*	*11.2% (138)*
Do you belief in the power of witchcraft, voodoo or the occult?	*20*	*POS*	*27.3% (337)*
Do you ever feel that people look at you oddly because of your appearance?	*22*	*POS*	*34.2% (422)*
Do you ever feel as if the thoughts in your head are being taken away from you?	*24*	*POS*	*3.9% (48)*
Do you ever feel as if the thoughts in your head are not your own?	*26*	*POS*	*7.3% (90)*
Have your thoughts ever been so vivid that you were worried other people would hear them?	*28*	*POS*	*10.6% (131)*
Do you ever hear your own thoughts being echoed back to you?	*30*	*POS*	*9.1% (112)*
Do you ever feel as if you are under the control of some force or power other than yourself?	*31*	*POS*	*5.3% (66)*
Do you ever hear voices when you are alone?	*33*	*POS*	*6.8% (84)*
Do you ever hear voices talking to each other when you are alone?	*34*	*POS*	*1.9% (23)*
Do you ever feel that you are not a very animated person?	*3*	*NEG*	*44.8% (553)*
Do you ever feel that you are not much of a talker when you are conversing with other people?	*4*	*NEG*	*51.8% (640)*
Do you ever feel that you experience few or no emotions at important events?	*8*	*NEG*	*38.1% (470)*
Do you ever feel that you have no interest to be with other people?	*16*	*NEG*	*50.2% (620)*
Do you ever feel that you are lacking in motivation to do things?	*18*	*NEG*	*67.2% (830)*
Do you ever feel that you are lacking in energy?	*21*	*NEG*	*70.9% (876)*
Do you ever feel that your mind is empty?	*23*	*NEG*	*24.6% (304)*
Do you ever feel that you are spending all your days doing nothing?	*25*	*NEG*	*42.6% (526)*
Do you ever feel that your feelings are lacking in intensity?	*27*	*NEG*	*26.2% (323)*
Do you ever feel that you are lacking in spontaneity?	*29*	*NEG*	*39.6% (489)*
Do you ever feel that your emotions are blunted?	*32*	*NEG*	*31% (383)*
Do you ever feel that you are neglecting your appearance or personal hygiene?	*35*	*NEG*	*27.3% (337)*
Do you ever feel that you can never get things done?	*36*	*NEG*	*55.1% (680)*
Do you ever feel that you have only few hobbies or interests?	*37*	*NEG*	*36.4% (450)*
Do you ever feel sad?	*1*	*DEP*	*93.7% (1,157)*
Do you ever feel pessimistic about everything?	*9*	*DEP*	*48.8% (603)*
Do you ever feel as if there is no future for you?	*12*	*DEP*	*27.5% (340)*
Do you ever feel as if you do not want to live anymore?	*14*	*DEP*	*24.9% (308)*
Do you ever cry about nothing?	*19*	*DEP*	*34.9% (431)*
Do you ever feel guilty?	*38*	*DEP*	*73.4% (907)*
Do you ever feel like a failure?	*39*	*DEP*	*48.1% (594)*
Do you ever feel tense?	*40*	*DEP*	*81.2% (1,003)*

Supplementary Figure S1
Path diagrams of the five psychotic experiences' models

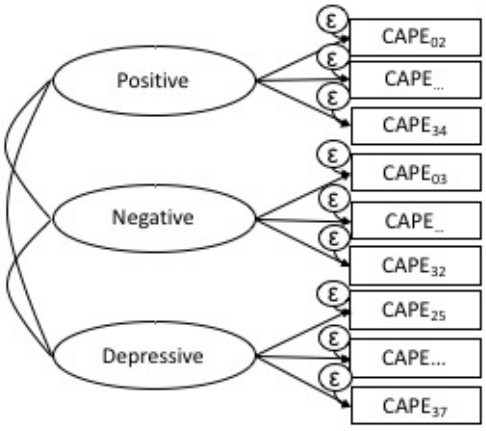
Model A



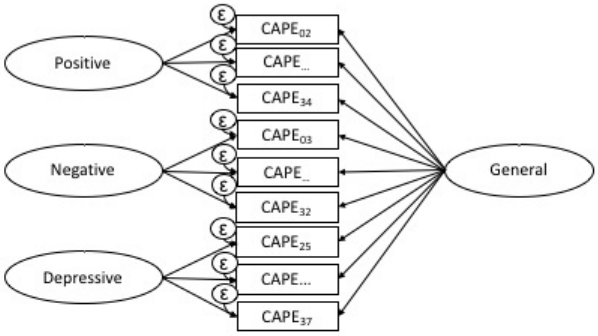
Model B



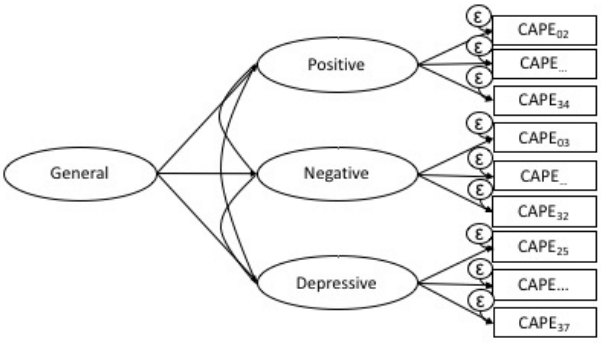
Model C



Model D



Model E



Explanatory note: (▭) Observed symptoms (CAPE items); (Ö) Unobserved variables (latent factors); (→) item loading on latent factors; (ε) item error variance. CAPE item numbers are showed in Tables S1; for simplicity, only three items for each latent factor are presented in the diagrams.

Explanatory note: *Model A*: unidimensional model with one unique general factor; *Model B*: multidimensional model with three uncorrelated specific factors; *Model C*: multidimensional model with three correlated specific factors; *Model D*: bifactor model with one general factor and three

uncorrelated specific factors; Model *E*: hierarchical model with three correlated first-order specific factors and one general second-order factor.
As showed in the main text and in Table 1, the bifactor model for the CAPE (Model D) best reflected the dimensional structure of psychosis in population controls when compared with the other models. This is consistent with our previous findings on the bifactor model for the OPCRIT in patients (Quattrone *et al.*, 2019). The bifactor model allows examining the variance due to each dimension whilst partitioning out the variance due to the common item effect of the whole symptomatology. Thus, in this study, we performed the best possible evaluation of the impact of cannabis use on specific subsets of psychotic symptoms or experiences in patients and controls.

Supplementary Table S4. Model fit statistics of unidimensional, multidimensional, bifactor, second-order models for psychotic experiences and for psychotic symptoms

CAPE (CONTROLS)				
	Full information fit statistics[a]			
	LL	AIC	BIC	SABIC
A - Unidimensional Model	-23638	47397	47715	47524
B - Multidimensional Model (three uncorrelated factors)	-23844	47808	48126	47936
C - Multidimensional Model (three correlated factors)	-23341	46808	47142	46942
D - Bifactor Model (one general factor and three specific uncorrelated factors)	-23139	46458	46935	46649
E - Hierarchical Model (three first-order specific correlated factors and one second order general factor)	-23341	46807	47135	46938
OPCRIT (PATIENTS) (Quattrone *et al.*, 2019)				
	Full information fit statistics[a]			
	LL	AIC	BIC	SABIC
A - Unidimensional Model	-29965	60126	60618	60306
B - Multidimensional Model (five uncorrelated factors)	-28070	56335	56826	56515
C - Multidimensional Model (five correlated factors)	-27894	56004	56546	56202
D - Bifactor Model (one general factor and five specific uncorrelated factors)	-27597	55489	56226	55759
E - Hierarchical Model (five first-order specific correlated factors and one second order general factor)	-27995	56197	56713	56386

LL, log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SABIC Sample-size Adjusted Bayesian Information Criterion
A difference of 10 in AIC, BIC and SABIC is considered important. Lower values indicate a statistically better model fit (best values across models are indicated in bold).

Supplementary Table S5. Prevalence of OPCRIT symptoms in patients (Quattrone *et al.*, 2019)

OPCRIT ITEM	Item no.	Factor	Valid frequency
Persecutory Delusions	54	POS	71.6% (794)
Well organised delusions	55	POS	41.6% (458)
Delusions of influence	58	POS	24.1% (267)
Bizarre Delusions	59	POS	23.3% (259)

Widespread Delusions	60	POS	42.4% (437)
Delusions of passivity	61	POS	15.2% (168)
Primary delusional perception	62	POS	26.2% (286)
Other primary delusions	63	POS	19.4% (213)
Delusions & hallucinations last for one week	64	POS	47.9% (495)
Persecutory delusions & hallucinations	65	POS	30.1% (311)
Thought insertion	66	POS	16.4% (180)
Thought broadcast	68	POS	15.5% (171)
Third person auditory hallucinations	73	POS	29.3% (322)
Running commentary voices	74	POS	24.1% (266)
Abusive/accusatory/persecutory voices	75	POS	31.8% (329)
Other (non-affective) auditory hallucinations	76	POS	23.3% (264)
Non-affective hallucination in any modality	77	POS	26.7% (294)
Negative formal thought disorder	29	NEG	19% (209)
Restricted affect	32	NEG	36.4% (404)
Blunted affect	33	NEG	21.9% (243)
Bizarre behaviour	17	DIS	44.9% (496)
Speech difficult to understand	26	DIS	20.9% (230)
Incoherent	27	DIS	13% (13)
Positive formal thought disorder	28	DIS	24.3% (268)
Inappropriate affect	34	DIS	19.6% (216)
Excessive activity	19	MAN	25.5% (283)
Reckless activity	20	MAN	21% (233)
Distractibility	21	MAN	47.4% (521)
Reduced need for sleep	22	MAN	30.8% (340)
Agitated activity	23	MAN	41.3% (457)
Pressured speech	30	MAN	23% (255)
Thoughts racing	31	MAN	33% (365)
Elevated mood	35	MAN	20.6% (229)
Irritable mood	36	MAN	47.7% (529)
Increased self esteem	56	MAN	24.1% (267)
Grandiose Delusions	57	MAN	23.3% (259)
Slowed activity	24	DEP	23.6% (261)
Loss of energy/tiredness	25	DEP	40.1% (444)
Dysphoria	37	DEP	48.7% (540)
Loss of pleasure	39	DEP	43.2% (477)
Poor concentration	41	DEP	61% (676)
Excessive self-reproach	42	DEP	25.8% (286)
Suicidal ideation	43	DEP	34.2% (380)
Initial insomnia	44	DEP	52.4% (576)
Middle insomnia (broken sleep)	45	DEP	38.4% (423)
Early morning waking	46	DEP	24.9% (274)
Excessive sleep	47	DEP	15.2% (168)
Poor appetite	48	DEP	37% (407)
Weight Loss	49	DEP	29.3% (315)

Supplementary Table S6.1. Symptom dimensions in patients by frequency of use and potency of cannabis[a]

Model	Lifetime frequency of use B (95% CI)		Potency of cannabis B (95% CI)	
	Less than daily *(v. never used)*	Daily *(v. never used)*	low potency *(v. no use)*	high potency *(v. no use)*
Positive symptom dimension	0.1 (-0.21 to 0.22)	0.23** (0.07 to 0.39)	0.09 (-0.12 to 0.28)	0.22** (0.02 to 0.29)
Negative symptom dimension	-0.07 (-0.29 to 0.15)	-0.09 (-0.26 to 0.09)	-0.24** (-0.41 to -0.06)	-0.2* (-0.39 to -0.02)
Depressive symptom dimension	-0.12 (-0.31 to 0.06)	-0.1 (-0.24 to 0.04)	-0.13 (-0.28 to 0.03)	-0.13 (-0.29 to 0.03)
Disorganization symptom dimension	0.26* (0.05 to 0.47)	0.11 (-0.04 to 0.27)	-0.02 (-0.19 to 0.15)	0.13 (-0.04 to 0.32)
Manic symptom dimension	0.02 (-0.17 to 0.22)	0.13 (-0.02 to 0.28)	0.23** (0.06 to 0.39)	0.27** (0.1 to 0.44)
General Psychosis factor	0.17* (0.01 to 0.33)	0.12* (0.01 to 0.25)	0.06 (-0.07 to 0.19)	0.02 (-0.12 to 0.17)

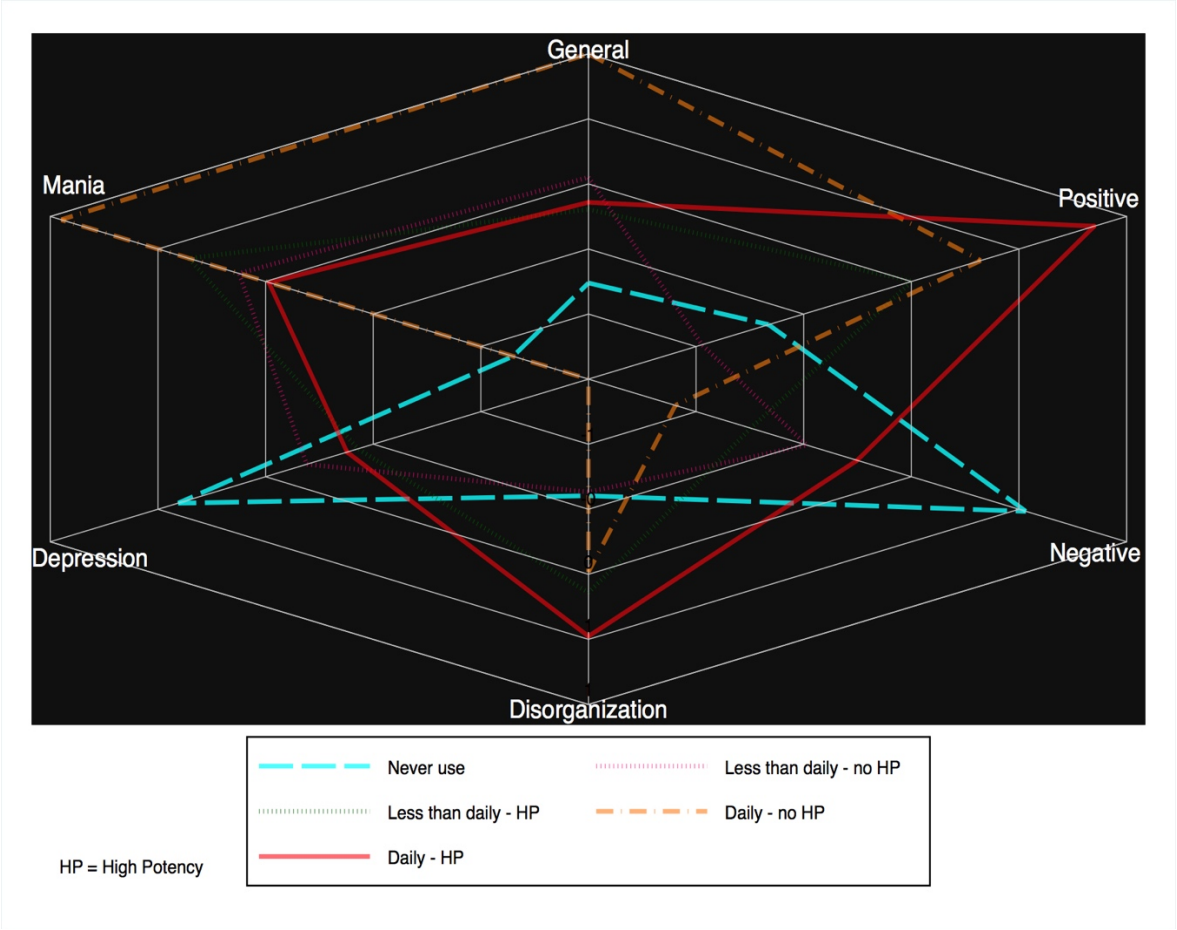
[a]All models were adjusted for age, sex, ethnicity, current use of other recreational/illicit substances, and diagnosis. Models were random-intercept models that included two random effects to allow symptomatology to vary across countries and across sites within countries but assumed that individual-level exposure to cannabis had a fixed effect across the entire sample.
Significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; associations that hold after Benjamini-Hochberg procedure are showed in bold.

Supplementary Table S6.2. Psychotic experience dimensions in controls by frequency of use and potency of cannabis[a]

Model	Lifetime frequency of use B (95% CI)		Potency of cannabis B (95% CI)	
	Less than daily *(v. never used)*	Daily use *(v. rare and never use)*	Low Potency *v. no use*	High potency *v. no use*
Positive psychotic experience dimension	0.04 (-0.08 to 0.16)	0.17 (-0.05 to 0.38)	0.08 (-0.06 to 0.22)	0.03 (-0.13 to 0.19)
Negative experience dimension	0.11 (-0.02 to 0.24)	0.14 (-0.09 to 0.38)	0.09 (-0.05 to 0.24)	0.12 (-0.05 to 0.29)
Depressive experience dimension	0.08 (-0.05 to 0.2)	0.17 (-0.08 to 0.4)	0.08 (-0.07 to 0.23)	0.05 (-0.11 to 0.22)
General psychotic experience factor	0.03 (-0.1 to 0.16)	0.13 (-0.11 to 0.37)	0.08 (-0.07 to 0.23)	-0.02 (-0.19 to 0.15)

[a]All models were adjusted for age, sex, ethnicity, current use of other recreational/illicit substances. Models were random-intercept models that included two random effects to allow symptomatology to vary across countries and across sites within countries but assumed that individual-level exposure to cannabis had a fixed effect across the entire sample.
Significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary Figure S2. Symptom dimensions by frequency of use and potency of cannabis



Chapter 6: Study 3

This paper uses genetic epidemiology and cannabis use data to examine the latent structure of psychosis. The study aimed to calculate PRSs for schizophrenia, bipolar disorder, and combined schizophrenia-bipolar disorder and to determine whether the variants conferring psychosis risk were also associated with the different expression of psychosis. Furthermore, the study aimed to examine whether the previously reported associations between cannabis use and the positive dimensions, in both FEP patients and controls, held when taking into account SZ-PRS. Overall, establishing coherence between symptom dimensions and genetic and environmental risk factors would confer validity to symptom dimensions as alternative phenotypes in the field of psychosis. Table 3 reports the summary of aims and hypotheses for study 3.

Table 3. Summary of aims and hypothesis for study 3

Aims	Hypothesis	Grounds for the hypothesis	Analytic approach
To examine the genetic population structure of the EU-GEI sample	N/A	N/A	Iterative pruning principal component analysis (ipPCA) of SNPs, using different packages in R
To calculate schizophrenia, bipolar disorder, and combined schizophrenia-bipolar disorder PRSs	N/A	N/A	Clumping and thresholding method (C+T) in PRSice

To examine the relationship between latent factors of psychosis at FEP and PRS	SZ PRS is associated with more negative symptoms at FEP	Heritability studies show that negative symptoms are the most heritable dimension of schizophrenia	Linear regression modelling in STATA 15
	SZ PRS is associated with more positive symptoms at FEP	SZ-PRS composite score also includes dopaminergic risk variants (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), the final common pathway towards experiencing positive symptoms (Edwards *et al.*, 2016)	
	BP PRS is associated with more manic symptoms at FEP	BP-PRS would confer a modifier-effect towards manic presentation at FEP (Bipolar Disorder Schizophrenia Working Group of the Psychiatric Genomics Consortium and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018)	
To examine the relationship between latent factors of psychosis in the general population and PRS	SZ-PRS would be positively associated with psychotic experiences	Genetic risk factors contribute to the continuity of psychotic experiences in the general population (Legge *et al.*, 2019b)	Linear regression modelling in STATA 15
To examine whether cannabis use is associated with more psychotic symptoms and experiences when taking SZ PRS into account	Both cannabis use and SZ-PRS are independently associated with positive psychotic experiences and symptoms.	Both genes and environmental factors contribute to the expression of psychosis	Linear regression modelling in STATA 15

6.1 Schizophrenia polygenic risk score and cannabis use modify psychosis expression in first episode psychosis patients and population controls

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Abstract

Background

Diagnostic categories within the psychosis spectrum are widely used in clinical practice, however psychosis may occur on a continuum. Therefore, we explored

whether the continuous distribution of psychotic symptoms across categories is a function of genetic as well as environmental risk factors, such as polygenic risk score (PRS) and cannabis use.

Methods

As part of the EU-GEI study, we genotyped first episode psychosis patients (FEP) and population controls, for whom transdiagnostic dimensions of psychotic symptoms or experiences were generated using item response bi-factor modelling. Linear regression was used, separately in patients and controls, to test the associations between these dimensions and schizophrenia (SZ) PRS, as well as the combined effect of SZ-PRS and cannabis use on the positive symptom/experience dimensions.

Results

SZ-PRS was associated with negative (B=0.18; 95%CI 0.03 to 0.34) and positive (B=0.19; 95%CI 0.03 to 0.36) symptom dimensions in 617 FEP, and with all the psychotic experience dimensions in 979 controls. The putative effect of SZ-PRS on either symptom or experience dimensions was of a small magnitude. Cannabis use was additionally associated with the positive dimensions both in FEP (B=0.31; 95%CI 0.11 to 0.52) and in controls (B=0.26; 95%CI 0.06 to 0.46), independently from SZ-PRS.

Conclusions

We report two validators to the latent dimensional structure of psychosis. SZ risk variants and cannabis use independently map onto specific dimensions, contributing to variation across the psychosis continuum. Findings support the hypothesis that psychotic experiences have similar biological substrates as clinical disorders.

Introduction

Psychotic disorders are syndromes caused by multiple genetic and socioenvironmental factors (1). However, the current classification system is based on a ‘natural history approach’ rather than on a ‘natural classification’ (2). Specifically, diagnostic categories of non-affective (e.g., schizophrenia, schizoaffective disorders) and affective (e.g., bipolar disorder, psychotic depression) psychosis were developed from observed similarities and dissimilarities of signs and

symptoms over time, without considering biological or socio-environmental factors (3). Hence, the question of whether current diagnostic categories are the most valid phenotypes for research is still debated, due to the following methodological limitations.

First, psychotic disorders are commonly studied as binary phenotypes (e.g., diagnosis yes/no), although psychotic symptoms follow a continuous distribution (4). Furthermore, some authorities claim that the introduction of operationalised classification systems in the 1970s led to the 'death of phenomenology' driving biological psychiatry to focus on the presence/absence of a diagnosis whilst overlooking the complex expression of psychotic phenomena (5).
Moreover, Kraepelin's paradigm (i.e., the neat distinction between non-affective and affective psychosis) has been challenged (6), though not yet replaced (3). As a consequence, the high comorbidity indices among psychotic disorders (7), as well as their high genetic correlation (8), may be an artefact of our own diagnostic conceptualization.

To address these limitations, the use an approach based on symptom dimensions has been proposed (9). Consistent with this methodology, we reported that transdiagnostic psychopathology at first episode psychosis (FEP) can be represented by a general psychosis factor (G), and five specific dimensions of positive (POS), negative (NEG), disorganization (DIS), manic (MAN), and depressive (DEP) symptoms (10). Similarly, a model composed of general and specific experience dimensions has been proposed to measure subclinical psychosis in the general population (11, 12). These conceptualizations statistically reflect a 'bi-factor

model', where the general and specific dimensions account, respectively, for the unidimensional and multidimensional nature of the latent psychosis construct (13, 14). We have previously advocated that such structures should be validated by the degree to which biological and environmental factors cohere with general and specific symptom dimensions (10). Indeed, according to the coherence theory of truth, psychiatric constructs can be approximated as true if they are well connected and integrated into our accumulated scientific evidence (15).

Thus, we recently found evidence that cannabis-associated psychopathology at psychosis onset is characterised by high POS scores and low NEG scores (16).
In relation to biological factors, symptom dimensions have been investigated in family, twin and adoption studies (17-22), overall showing that NEG or DIS symptoms had higher familial aggregation than other symptom dimensions.
In recent years the availability of summary statistics from large genome-wide association studies (GWAS) across psychiatric phenotypes has allowed researchers to test in independent samples how the genetic liability to a disorder predicts any other traits (23). Genetic liability is commonly summarised into a polygenic risk score (PRS) (24), however, only a few studies to date have investigated the relation between SZ-PRS and psychotic symptom dimensions (25). In patients, an association between SZ-PRS and NEG (or DIS) symptoms was found in several SZ studies (26-28) and in Psychiatric Genomics Consortium (PGC) large mega-analyses (29, 30). However, other studies have not found the same pattern of associations (31, 32), and only one study reported that SZ-PRS correlated with POS symptoms (28). Interestingly, in the general population an association was observed

between SZ-PRS and either NEG (12, 33) or POS psychotic experiences (34-36); however, negative findings have also been reported (37).

The inconsistency across studies could be explained by differences in study design, methods, and GWAS power. Of note, only one small study examined a FEP sample (38), in which confounding effects of antipsychotic drugs on symptoms are minimised and a common comparable time point in the course of illness is used. In addition, most studies have not performed factor analysis of observed symptoms to measure and validate latent constructs. Finally, no studies have applied summary statistics from recent PGC GWAS investigating similarities and dissimilarities between SZ and BP (29).

We have previously reported findings from bi-factor models of 1) psychotic symptoms in a multinational FEP sample (10) and 2) psychotic experiences in controls representative of the population at risk in each catchment area (11). In the current study, we aimed to investigate the association between these phenotypes and genetic loading for SZ and BP, as summarised by i) SZ-PRS, ii) BP-PRS, iii) combined SZ & BP- PRS. We further explored whether the previously reported association of cannabis use with the POS dimensions (16) holds when taking into account SZ-PRS.

Based on an *a priori* synopsis, we hypothesized that SZ-PRS would be positively associated with the NEG dimension in FEP patients, and with the POS dimensions in both FEP patients and the general population. Furthermore, we hypothesized a cumulative effect of cannabis use on POS dimensions independent of SZ-PRS.

Finally, we expected in FEP, an association between BP-PRS and the MAN symptom dimension, and between the combined SZ & BP- PRS and the G factor.

Methods and Materials

Sample design and procedures

FEP patients and population controls were recruited as part of the EUropean network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI). FEP patients were identified between 2010 and 2015 across six countries to examine incidence rates of psychotic disorders and patterns of symptomatology (10, 39). For examining biological and environmental risk factors, DNA samples were collected, and an extensive face-to-face assessment was conducted on 1,130 FEP and 1,497 controls, broadly representative of the population living in each catchment area by age, sex and ethnic group. All participants provided informed, written consent. Ethical approval was provided from local research ethics committees in each catchment area: South London and Maudsley and Institute of Psychiatry Research Ethics Committee; National Research Ethics Service Committee East of England–East Cambridge; Medisch-Ethische Toetsingscommissie van het Academisch Centrum te Amsterdam; Comité Ético de Investigación Clínica Hospital Gregorio Marañón; Comité Ético de Investigación Clínica del Hospital Clinic de Barcelona; Comité Ético de Investigación Clínica del Hospital Clinic Universitari de Valencia; Comité Ética de la Investigación Clínica del Principado de Asturias; Comité Ético de Investigación Clínica de Galicia; Comité Ético de Investigación Clínica del Hospital Virgen de la Luz de Cuenca; Comité de Protéction des Personnes–CPP Île de France IX; Comitato Etico Policlinico S Orsola Malpighi; Comitato Etico Azienda Ospedaleria Universitaria di Verona; Comitato Etico Palermo 1, Azienda Ospedaliera

Policlinico “Paolo Giaccone”; and Research Ethics Committee of the clinical Hospital of Ribeirão Preto Medical School, University of São Paulo, Brazil. More information on recruitment strategies is available in earlier EU-GEI incidence and case-control papers (39, 40).

Measures

Data on age, sex, and ethnicity were collected using a modified version of the Medical Research Council Sociodemographic Schedule (41).

The OPerational CRITeria (OPCRIT) system (42) was used by centrally trained investigators, whose reliability was assessed before and throughout the study (k=0.7), to assess psychopathology experienced in the first four weeks after FEP and define research-based diagnoses. Moreover, psychopathology assessment included the use of the Schedule for Deficit Syndrome (SDS) (43) to evaluate NEG symptoms, which are not extensively covered by the OPCRIT.

The Community Assessment of Psychic Experiences (CAPE) (44) was administered to population controls to report their positive, negative, and depressive psychotic experiences.

A modified version of the Cannabis Experience Questionnaire ($CEQ_{EU\text{-}GEI}$) (45) was used to collect extensive information on patterns of cannabis use.

Dimensions of psychotic symptoms and experiences

Data from OPCRIT and CAPE were analysed using item response modelling in M*plus*, version 7.4, to estimate two bifactor models of psychopathology, based on the associations among observer ratings of psychotic symptoms in patients or self-rating of psychotic experiences in controls (Supplementary Figures S1 and S2). This

methodology is described in full in earlier EU-GEI papers on transdiagnostic dimensions (10, 11). Briefly, OPCRIT and CAPE items were dichotomized as 0 '*absent'* or 1 '*present'*, and two different bi-factor models were estimated for patients and controls. Bi-factor solutions were compared with three competitive solutions (i.e., unidimensional, multidimensional, hierarchical models of psychosis) using, as model fit statistics, Log-Likelihood (LL), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Sample-size Adjusted BIC (SABIC). McDonald's omega (ω) (46), omega hierarchical (ω_H) (46), and index *H* (47), were used as reliability and strength indices.

Data from SDS were analysed in M*plus*, version 7.4, following the same procedure as described above. We did not estimate a bi-factor model for SDS due to lack of rationale for a G factor of negative symptoms. Instead, based on the structure of the NEG construct (48) and previous factor analysis studies on SDS (49), we estimated a multidimensional model of NEG symptoms composed of the two specific dimensions of 1) 'avolition' and 2) (lack of) 'emotional expressivity'. We considered 'emotional expressivity' as the most genuine phenotypic expression of primary negative symptoms for subsequent analysis, as the behavioural manifestation of 'avolition' may partly overlap with depressive symptoms in a FEP sample. SDS was not administered in one of the study sites, Verona, which was therefore not included in the analysis of NEG symptoms.

Genotype procedure

The EU-GEI case-control sample was genotyped at the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff (UK) using a custom Illumina HumanCoreExome-24 BeadChip genotyping array covering 570,038 genetic

variants. Imputation was performed in the Michigan Imputation Server, using the Haplotype Reference Consortium reference panel, with Eagle software for estimating haplotype phase, and Minimac3 for genotype imputation (50-52). The imputed best-guess genotype was used for the present analysis.

Population stratification and polygenic risk score calculation

We performed a two-step procedure to account for the multi-ethnic nature of the sample (reported in full in the supplementary material), by excluding populations in our sample of very different ancestry from external GWAS data. Briefly, as a first step, we identified in our sample ancestry clusters of individuals through iterative pruning of principal component analysis (ipPCA) of single nucleotide polymorphisms (SNPs), and we tested for each cluster whether PRS discriminated cases from controls. As a second step, we merged these clusters (based on whether PRS had discriminative value), removed long-range genome regions with complex linkage disequilibrium (LD) patterns, recalculated main Principal Components (PCs), and finally constructed main PRSs using PRSice (53). Specifically, individuals' risk variants were weighted by the log(odds ratio), where the odds ratio was extracted from the latest summary statistics of SZ and BP PGC mega-analyses (29, 54, 55), which did not include any EU-GEI sample. Logistic regression was then applied to predict case status from SZ- and BP-PRS, after covarying for 10 PCs, sex, age, and primary diagnosis. Nagelkerke's R^2 was used as a measure of the difference in variance between the full-model versus a model with the covariates alone, at the SNPs p-value threshold (P_T)=0.05 (selected *a priori* as it maximised the explained variance in case status in the PGC studies (54, 55)).

Relationship between symptom dimensions, polygenic risk scores, and cannabis use

We tested for associations between PRSs and the scores on transdiagnostic dimensions of psychotic symptoms/experiences, separately in FEP and controls, using linear regression.

Specifically, in FEP we tested for association between all symptom dimensions and the three PRSs. In controls, we tested for association between all psychotic experience dimensions and SZ-PRS; we did not test BP-related PRSs since (hypo)manic experiences were not rated in our controls.

Moreover, we used predicted values of SZ-PRS after regression of case/control status, to illustrate the continuous distribution of SZ-PRS in our sample according to quartiles of positive psychotic experience and symptoms.

To examine the combined associations of cannabis use and SZ-PRS with POS dimensions, we selected the two variables on pattern of cannabis use previously associated with POS (11), i.e., 'lifetime daily use' in patients and 'current use' in controls. We first checked for correlation with SZ-PRS, and subsequently we added the two cannabis terms to the models.

All analyses were adjusted for sex, gender, 10 ancestry principal components, study site, and diagnostic category. Given the high number of outcomes (six dimensions in patients, four in controls) and predictors (PRSs and cannabis use), and the number of hypotheses (four in patients, one in controls), we controlled the false discovery rate using the Benjamini and Hochberg procedure (56), tolerating a 10% false discovery rate (q=0.10). Furthermore, as a sensitivity measure, in PRSice we tested whether the main effect of PRSs on dimensions held at other P_T and ran a permutation analysis to further control the familywise error rate, by repeating the PRSice procedure shuffling the phenotype 5,000 times to obtain an empirical

distribution of the p-value at the best P_T. Finally, we used AVENGEME (Additive Variance Explained and Number of Genetic Effects Method of Estimation) to further evaluate the consistency of the effect directions across different P_T and compute the genetic covariance (σ12) between our symptom dimensions and the PGC GWAS data (57).

Results

Main PCs and PRS computation

Population stratification findings are presented in the supplement material. Based on the case-control discriminative value of SZ- and BP-PRS in each population cluster, we merged 1,596 individuals (617 FEP and 979 population controls) for SZ-PRS analyses, and 505 FEP for BP-PRS analysis only. The ability of SZ and BP PRSs to distinguish cases from controls in the main sample is presented in Figure 1, showing that at P_T=0.05, SZ-PRS accounted for a Nagelkerke's R^2 of 0.09 ($p=6.9x10^{-26}$); and BP-PRS for a Nagelkerke's R^2 of 0.02 ($p=5x10^{-6}$).

Psychotic symptom dimensions by PRS in patients

Findings on symptom dimensions in cases by SZ-, BP-, and SZ & BP- PRSs at P_T=0.05 are shown in Table 1 and Figure 1. As expected in PRS cross-trait predictions (23), the magnitude of the SNPs effect was small for all the associations detected. Specifically, SZ-PRS was associated with a high score for both the positive (B=0.19, 95% CI 0.03 to 0.35; Nagelkerke's R^2 =0.009, p=0.019) and negative (B=0.18, 95% CI 0.03 to 0.33; Nagelkerke's R^2 =0.01, p=0.021) symptom dimensions. Moreover, we found no nominal association between BP-PRS and the MAN symptom dimension (B=0.09, 95% CI -0.01 to 0.19; Nagelkerke's R^2 =0.008,

p=0.055); and between SZ & BP- PRS and the G factor (B=0.06, 95%CI -0.05 to 0.16; p=0.158).

Sensitivity analysis showed that the pattern of associations between SZ-PRS with either POS or NEG symptom dimensions was consistently observed across all P_T and remained relevant even after permutation analysis (Figure S7 – supplement, showing empirical p-values of 0.007 for POS; and of 0.055 for NEG). Furthermore, a positive genetic covariance was observed between both NEG and PGC SZ GWAS [σ12=0.56 (95%CI 0.39 to 0.76)] and POS and PGC SZ GWAS [σ12=0.51 (95%CI 0.35 to 0.69)].

Finally, the violin plots presented in Figure 2 illustrate the kernel distribution of predicted value of SZ-PRS across individual quartiles of positive psychotic symptoms.

Psychotic experience dimensions by SZ-PRS in controls

A positive association between SZ-PRS with a higher score at all psychotic experience dimensions was found (Table 2). Sensitivity analysis showed that the association between SZ-PRS with POS psychotic experiences was consistent across different P_T and remained relevant after permutation analysis (Figure S8 – supplement, showing an empirical P-value = 0.003). The kernel distribution of predicted value of SZ-PRS according to individual quartiles of psychotic experiences in controls is reported in Figure 3.

POS symptom dimensions by PRS and cannabis use in patients and controls

Daily cannabis use (B=0.31; 95%CI 0.11 to 0.52; p=0.002) and SZ-PRS (B=0.22; 95%CI 0.04 to 0.39; p=0.014) were independently associated with POS symptoms in

patients, and this joint model improved fit over a model with SZ-PRS alone (LR chi2(1)=6.10, p = 0.01).

Similar results were found for POS psychotic experiences in controls, with main effects of current use of cannabis (B=0.26, 95%CI 0.06 to 0.46; p=0.011) and SZ-PRS (B=0.13, 95%CI 0.02 to 0.25; p=0.022) (Figure 4), and with an improvement of model fit (LR chi2(1)=6.42, p = 0.01).

Discussion

Principal findings

This is the first study to investigate the combined effect of SZ-PRS and cannabis use on psychosis dimensions. We found that these two factors, independently from each other, are associated with more clinical and sub-clinical POS symptoms in both FEP patients and controls. Moreover, we found a relationship between SZ-PRS and more NEG symptoms and experiences. Finally, we did not find in our sample an association between BP-PRS and MAN symptoms; or between the combined SZ & BP- PRS and the G factor.

Our findings provide first evidence that in patients and controls, the latent structure of psychosis, as generated using a statistically guided approach, is valid and coheres with both SZ risk variants and cannabis use. However, any further interpretation on the applicability of these findings should take into account the small magnitude of all the detected associations.

Comparison with previous research

Our findings extend those from previous research on the validity of psychosis symptom dimensions by ascertaining their coherence with genetic factors and

cannabis use. First, under the hypothesis that psychosis symptom presentation is partly a function of SZ genetic liability, we reported an association between SZ-PRS and both POS and NEG symptom dimensions. This in line with a meta-analysis suggesting that different SZ risk loci impact on SZ clinical heterogeneity, e.g. genes related to immune system might be overrepresented for NEG, and genes related to addiction and dopamine-synapses might be overrepresented for POS (58). Familial co-aggregation of NEG symptoms was reported in the Danish adoption study (19), in the Roscommon family study (59), in the Maudsley twin series studies (18). Genome-wide suggestive linkages with an effect on NEG symptoms have also been reported, although without reaching a significance threshold (60, 61). GWAS and PRS examinations provide good evidence of a polygenic signal for NEG (26-30). Altogether, these studies provide converging evidence that NEG has substantive heritability at least partly due to cumulative schizophrenia risk loci. The DIS dimension has also been reported as having high heritability in some studies (20), but we found no evidence of its association with SZ-PRS in our FEP sample, and we could not examine this latent construct in our controls. Speculatively, it is possible that DIS symptom differ in their lifetime v. FEP prevalence, or that genetic loci influencing DIS are different from those carrying SZ risk (20).

Second, our results on the relationship between SZ-PRS and POS are intriguing but less consistent with previous literature. Possible familial co-aggregation of POS symptoms was rarely reported (62, 63). However, a previous study observed that BP patients with higher SZ-PRS presented with more mood-incongruent POS symptoms (64), which suggests SZ-PRS has a POS modifier effect. Nevertheless, this was not confirmed by meta-analysis of PGC and GPC samples (30, 65). We may consider in

interpreting our data, that the EU-GEI sample included FEP patients only, hence symptomatology rating was not confounded by antipsychotic treatment; whereas PGC and GPC samples are most chronic schizophrenia samples, where the enduring antipsychotic treatment can attenuate POS symptoms and increase NEG symptoms (i.e., secondary NEG symptoms). Moreover, various environmental factors impacting at different levels on dopaminergic activity makes it difficult to disentangle the risk variants contribution to POS symptoms over the course of SZ. From this perspective, we extend previous evidence that use of cannabis is associated with more POS symptomatology at FEP (11, 66), clarifying that this association is independent from SZ genetic risk loading.

Third, unlike our hypothesis and larger studies (29, 67), we did not report an association between BP-PRS and MAN. This may suggest that our sample is too small for BP-PRSs based on GWAS than SZ, or the true effect of BP-PRS is too small.

Fourth, we replicated in our controls the same patterns of associations as in cases between SZ-PRS and dimensions, but in the form of sub-clinical psychosis. Further, we provide novel evidence that SZ-PRS and current cannabis use are both associated with more POS psychotic experiences. It has been debated whether sub-clinical psychotic symptoms have an etiological overlap with full-blown psychosis. Our findings support the evidence that SZ-PRS correlates with psychotic experiences (35), which in adults may be reflecting similarities with biological SZ risk factors (35). Moreover, a few SNPs reaching genome-wide significance have been

recently identified for psychotic experiences, for example in *CNR2*, coding for the cannabinoid receptor type 2 (68). This suggests that further studies are needed to clarify the relationship between patterns of cannabis use and sets of genes potentially enhancing its psychotropic effects (69).

Finally, to our knowledge this is the first study examining SZ & BP- PRS and G factor in psychotic disorders, under the hypothesis they have a positive correlation. We report a negative finding which may be explained by G not properly reflecting general psychopathology in our FEP sample. On other hand, the G factor of psychotic experiences in controls well correlated with SZ genetic liability.

Limitations

The following limitations suggest exercising caution when interpreting our findings.

1) We performed extensive work for defining the fine-scale population structure in a multi-ethnic sample. Certainly, having a sample of individuals from a single homogenous population would have improved the quality of the analysis, however our study has the advantage of being more representative of the real clinical practice. Most important, we included as far as possible population clusters not located in Europe but still suitable for PRS analyses, which is in line with a more general aim of not contributing to healthy disparities (70).
2) Regarding symptom ratings in patients, we used symptom dimensions from two different scales, i.e. NEG from SDS, and the other symptom dimensions from OPCRIT. In the EU-GEI study, negative symptoms were rated through the administration of SDS; moreover, exploratory factor analyses of OPCRIT in other samples showed that a hybrid DIS/NEG dimension was often obtained rather than

discrete NEG and DIS dimensions (30, 71). Of note, our preliminary analysis of SZ-PRS and NEG using OPCRIT showed no nominal association (72), due, possibly, to the scarce item covariance coverage, acknowledged as a limitation in our earlier paper on symptom dimensions (10).

3) Regarding the bifactor solutions, G may be difficult to interpret and possibly overfits the data (73). Nevertheless, in our model, G improves the measurement of specific dimensions by making their score not unduly affected by the all-item covariance (10). Moreover, based on the strength of item factor loadings in our sample, G could be interpreted: 1) in patients, as combined manic-delusional symptomatology (10); 2) in controls, as a combined measure of all types of psychotic experiences (11).
4) We did not validate self-reported information on current use of cannabis with biological samples. However, this method does not allow ascertaining lifetime patterns of cannabis use (40) and is not considered a gold standard method (74). Moreover, it has been shown that self-report information on cannabis use is consistent with laboratory data (75).
5) We did not use a PRS based on GWAS of symptom dimensions, as this is currently unavailable. It is noteworthy that, genes conferring risk to a disorder ('risk genes') may not overlap with genes modifying symptom presentation ('modifier genes') (76), although it is hypothesised that there are genes with a mixed effect (58). Thus, our study answers the question whether the genetic liability for psychotic disorder explains variance of some phenotypic traits, without accounting for other possible genetic sources of that variance (i.e., the contribution of modifier genes, copy number variants, and rare SNPs).

Implications

Most clinical and research psychiatrists still embrace Kraepelin's nosology in the field of psychosis, despite the fact that for a century concerns have been raised related to the absence of converging validators to distinguish non-affective and affective psychotic disorders (77). We report two classes of external validators of transdiagnostic symptom dimensions, such as SZ-PRS and cannabis use. It should be born in mind that pharmacological and psychological interventions, as well as cannabis cessation and all secondary prevention strategies target particular symptoms more than the general diagnosis. Hence, our findings support the concept of a psychosis continuum

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Table 1. Symptom dimension scores by PRSs in cases

	General[a] B (95% CI)	Positive[a] B (95% CI)	Negative[b] B (95% CI)	Disorganization[a] B (95% CI)	Mania[a] B (95% CI)	Depression[a] B (95% CI)
SZ PRS model	0.04 (-0.09 to 0.18) p=0.528	0.19 (0.03 to 0.35) **p=0.021***†	0.16 (0.1 to 0.3) **p=0.019***†	-0.01 (-0.16 to 0.14) p=0.928	0.06 (-0.07 to 0.2) p=0.378	-0.06 (-0.2 to 0.07) p=0.350
BP PRS	0.06	0.05	-0.005	0.01	0.09	-0.01

model	(-0.03 to 0.15) p=0.175	(-0.06 to 0.17) p=0.341	(-0.09 to 0.08) p=0.915	(-0.1 to 0.1) p=0.976	(-0.01 to 0.19) p=0.055	(-0.1 to 0.08) p=0.938

Explanatory note. B, Unstandardized regression coefficient; CI, confidence interval. Covariates in multiple models were sex, age, ten ancestry PCs, and categorical diagnosis.
a. Symptom dimension scores from OPCRIT factor analysis.
b. Symptom dimension scores from SDS factor analysis.
Associations nominally significant after permutation analysis are showed in bold
*P-values nominally significant after Benjamini-Hochberg procedure at FDR threshold = 0.1
(†Benjamini-Hochberg P-value: 0.056)

Table 2. Psychotic experience dimension scores by SZ-PRS in controls

	General[a] B (95% CI)	Positive[a] B (95% CI)	Negative[a] B (95% CI)	Depression[a] B (95% CI)
SZ-PRS[1] model	0.19 (0.02 to 0.24) **p=0.003***††	0.14† (0.03 to 0.26) **p=0.016***†	0.18†† (0.05 to 0.3) **p=0.005***†	0.15† (0.03 to 0.27) **p=0.012***††

Explanatory note. B, Unstandardized regression coefficient; CI, confidence interval. Covariates in multiple models were sex, age, and ten ancestry PCs.
a. Psychotic experience dimension scores from CAPE factor analysis
Associations nominally significant after permutation analysis are showed in bold
*P-values nominally significant after Benjamini-Hochberg procedure at FDR threshold = 0.1
(†Benjamini-Hochberg P-value: 0.056; ††Benjamini-Hochberg P-value: 0.045)

Figure 1 - SZ-PRS and BP-PRS by FEP-control status

The bar plot shows the variance in case-control status (y-axis) explained by SZ-PRS (yellow) and BP-PRS (red) respectively. P-value is presented on top of the bars.

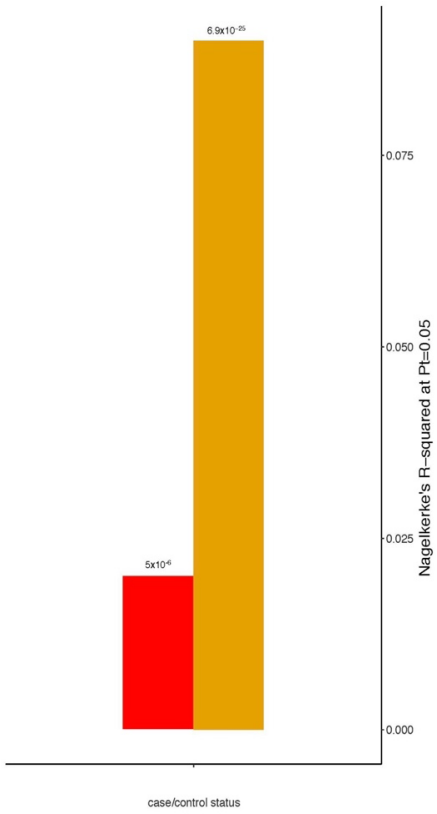


Figure 2 - SZ- PRS, BP- PRS, and SZ & BP- PRS by symptom dimensions in FEP

The bar plot shows the variance (y-axis, Nagelkerke's R^2) explained by the different PRSs (x-axis) for each symptom dimension (z-axis).

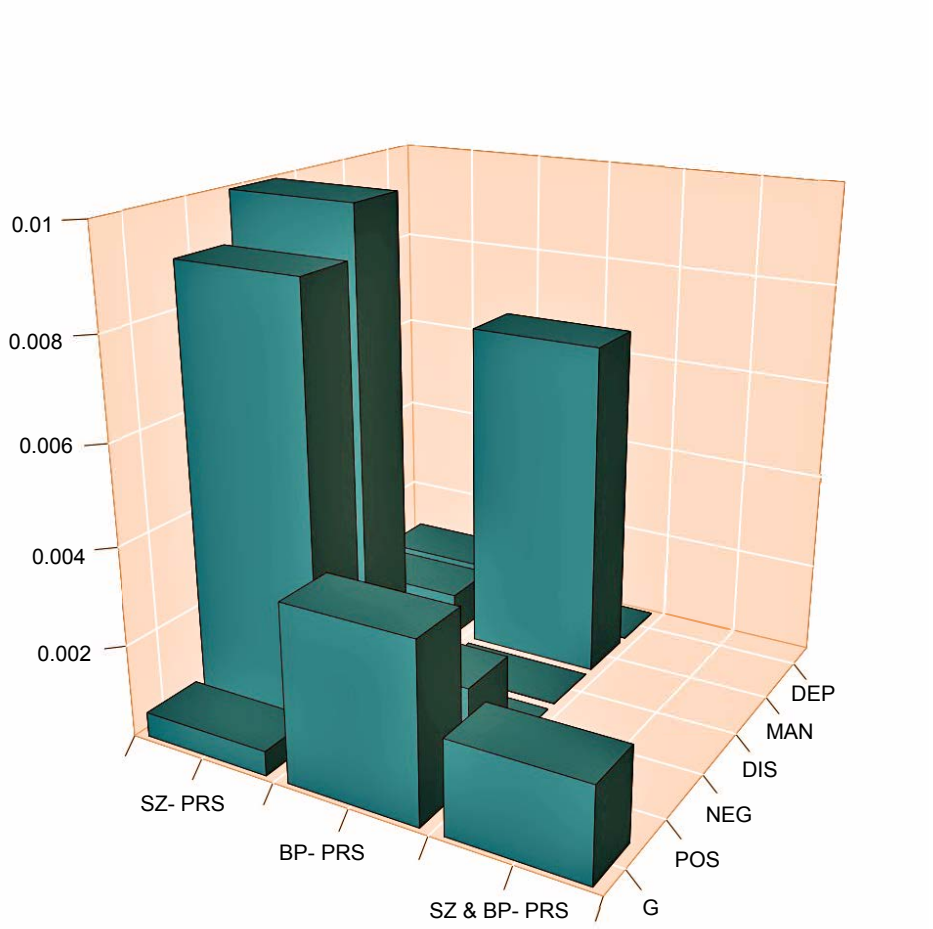


Figure 3 – Distribution of SZ-PRS according to quantiles of psychosis in the general population and separately in FEP patients

The violin plots show the distribution of SZ-PRS in the EU-GEI sample by individuals classified according to their score at POS experience dimension and symptom dimensions, separately in population controls (left side) and FEP patients (right side) at different quantiles.
In controls: (1) 0-25% psychotic experiences; (2) 25-75% psychotic experiences; and (3) 75-100% psychotic experiences.
In FEP: (4) 0-25% psychotic symptoms; (5) 25-75% psychotic symptoms; and (6) 75-100% psychotic symptoms.
Explanatory note: Interquartile range, 95% confidence interval, median and mean are illustrated within the bars. On each side of the bars is represented a kernel density estimation to show the distribution shape of the data.
Dots indicate current cannabis use in controls and daily cannabis use in patients (red=no; green=yes)

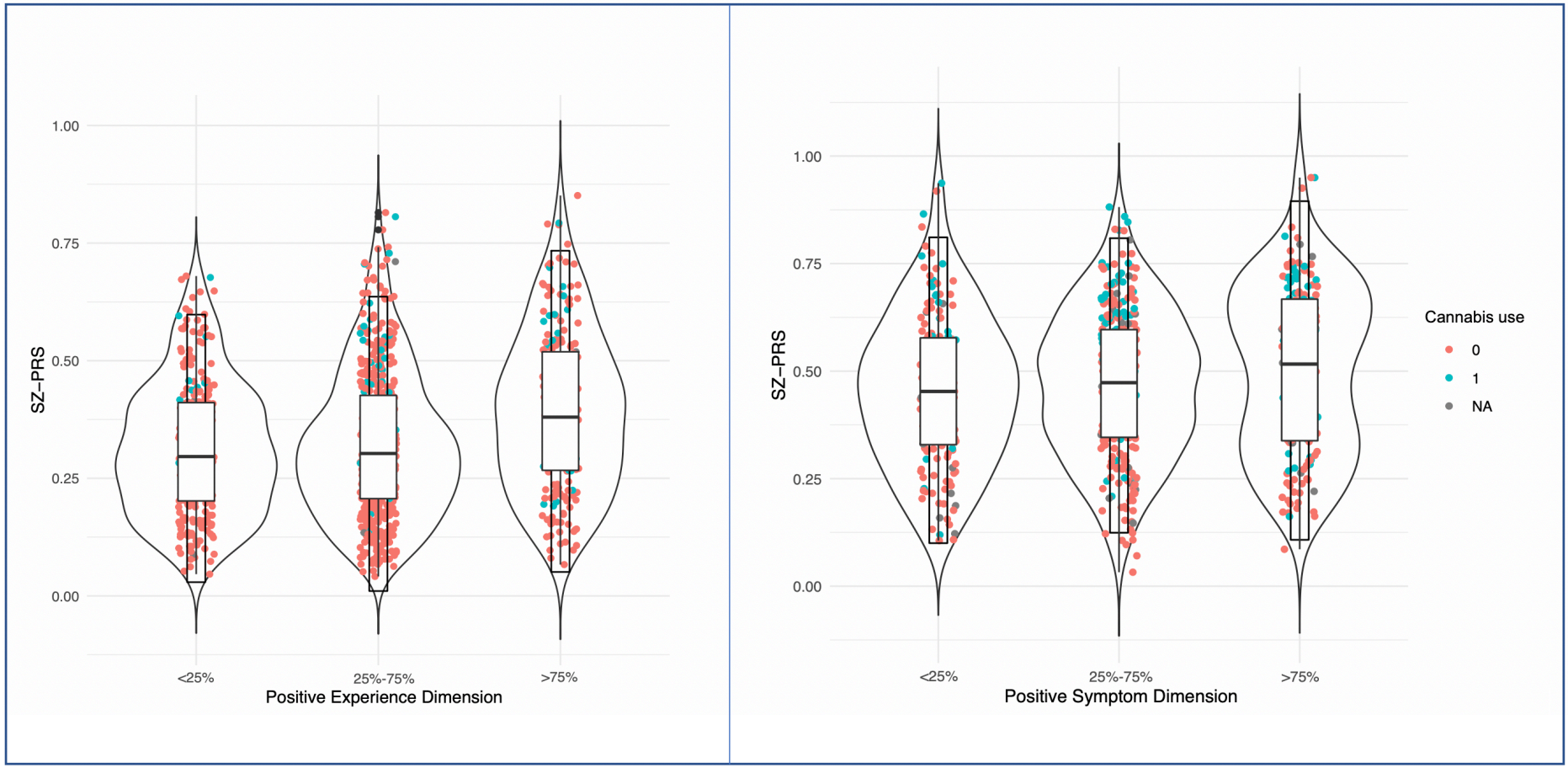
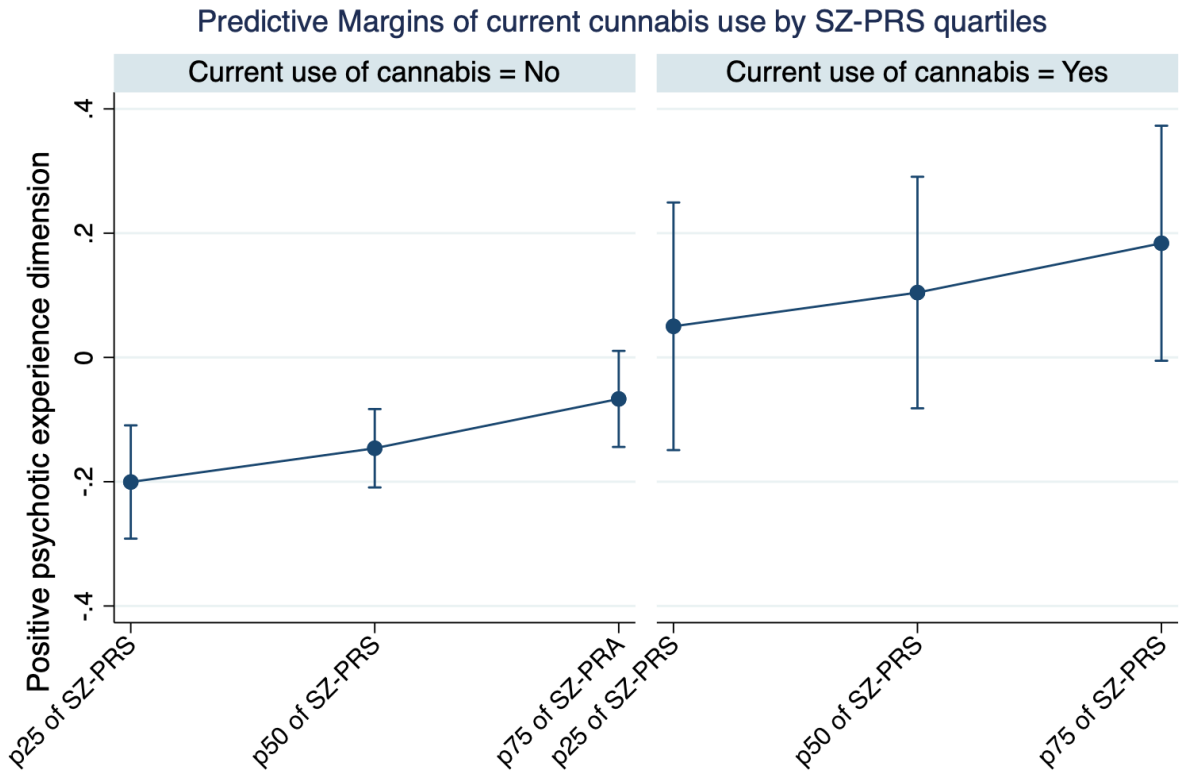


Figure 4 – POS dimensions by SZ-PRS and cannabis use in controls

The graph presents the predicted POS symptom dimension scores at two different covariate values (cannabis use yes/no), holding SZ-PRS at 25th, 50th, and 75th percentiles. Predicted values were adjusted for age, sex, and 10 ancestry PCs.



6.2 Study 3, supplementary material

TABLE S1

Sociodemographic and clinical differences between genotyped and not-genotyped individuals[1]

Case/control sample N=2,627 (N_{FEP}=1,130, $N_{controls}$=1,497)	GWAS - NO N=631 (N_{FEP}=308, $N_{controls}$=323)	GWAS - YES N=1,994 (N_{FEP}=822, $N_{controls}$=1,174)	Test statistics
Age			
Mean (SD)	32.8 (11.7)	34.4 (12.3)	t(2,2623)=2.8; p<0.005
Gender			
Male	292 (46.3)	932 (46.7)	$\chi^2(1)=0.03$; p=0.85
Self-reported Ethnicity			
White	420 (66.6)	1,473 (73.8)	$\chi^2(5)=13.5$; p<0.05
Black	92 (14.6)	212 (10.6)	
Mixed	62 (9.8)	164 (8.2)	
Asian	18 (2.9)	50 (2.5)	
North African	21 (3.3)	55 (2.8)	
Other	18 (2.8)	41 (2.1)	
Research Domain Criteria Diagnosis (case only sample)			
Bipolar disorder	14 (4.6)	46 (5.7)	$\chi^2(4)=4.04$; p=0.4
Major depression with psychotic features	18 (5.9)	32 (4)	
Schizophrenia	98 (32.3)	292 (36.1)	
Schizoaffective disorder	126 (41.6)	308 (38.1)	
Unspecified psychosis	48 (17.65)	131 (16.2)	

[1]Note: 9 samples were excluded at preliminary sample QC due to genotype-phenotype sex mismatch.

TABLE S2

Sociodemographic and clinical differences between individuals providing buccal or blood sample[1]

Case-control genotyped sample - N=1,994	Buccal N=298 (N_{FEP}=118, $N_{controls}$=180)	Blood N=1,696 (N_{FEP}=704, $N_{controls}$=994)	Test statistics
Age			
Mean (SD)	34.7 (12.4)	32.5 (11.4)	t(2,1992)=2.8; p<0.005
Gender			
Male	152 (53.7)	912 (51)	$\chi^2(1)=0.74$; p=0.38
Self-reported Ethnicity			
White	420 (66.6)	1,473 (73.8)	$\chi^2(5)=13.5$; p<0.05
Black	92 (14.6)	212 (10.6)	
Mixed	62 (9.8)	164 (8.2)	
Asian	18 (2.9)	50 (2.5)	
North African	21 (3.3)	55 (2.8)	
Other	18 (2.8)	41 (2.1)	
Research Domain Criteria Diagnosis (case only sample)			
Bipolar disorder	6 (5.1)	40 (5.1)	$\chi^2(4)=10.5$; p<0.05
Major depression with psychotic features	1 (0.9)	31 (4.5)	
Schizophrenia	41 (35)	251 (36.3)	
Schizoaffective disorder	57 (48.7)	251 (36.3)	
Unspecified psychosis	12 (10.3)	119 (17.2)	

[1]Note: 9 samples were excluded at preliminary sample QC due to genotype-phenotype sex mismatch.

Figure S1 Bi-factor model of psychopathology at FEP based on OPCRIT items (1)

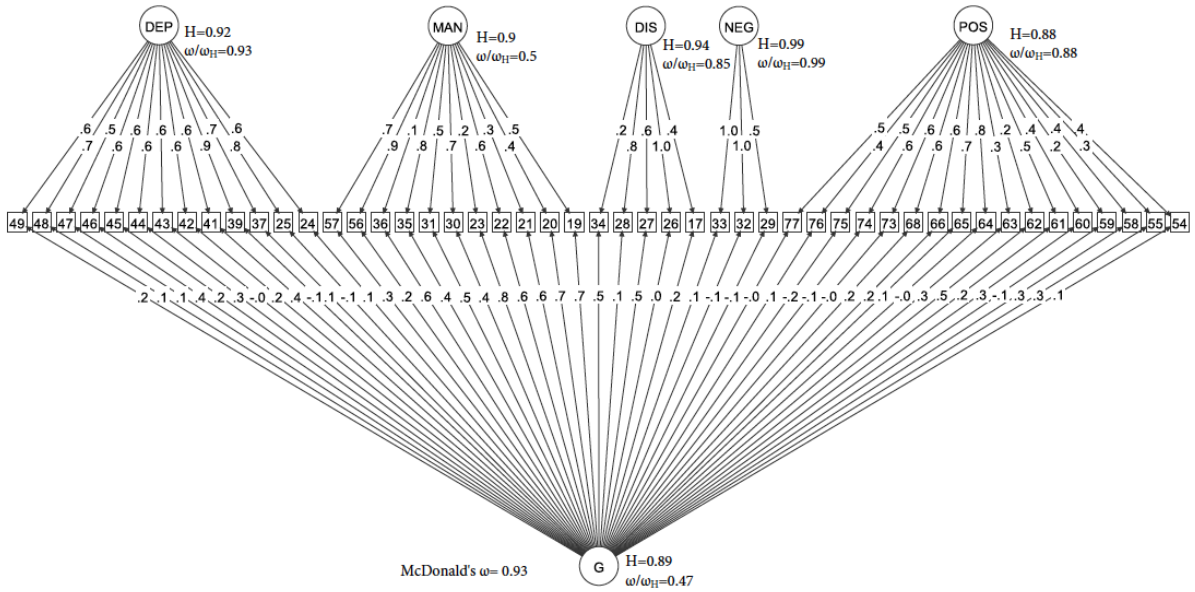
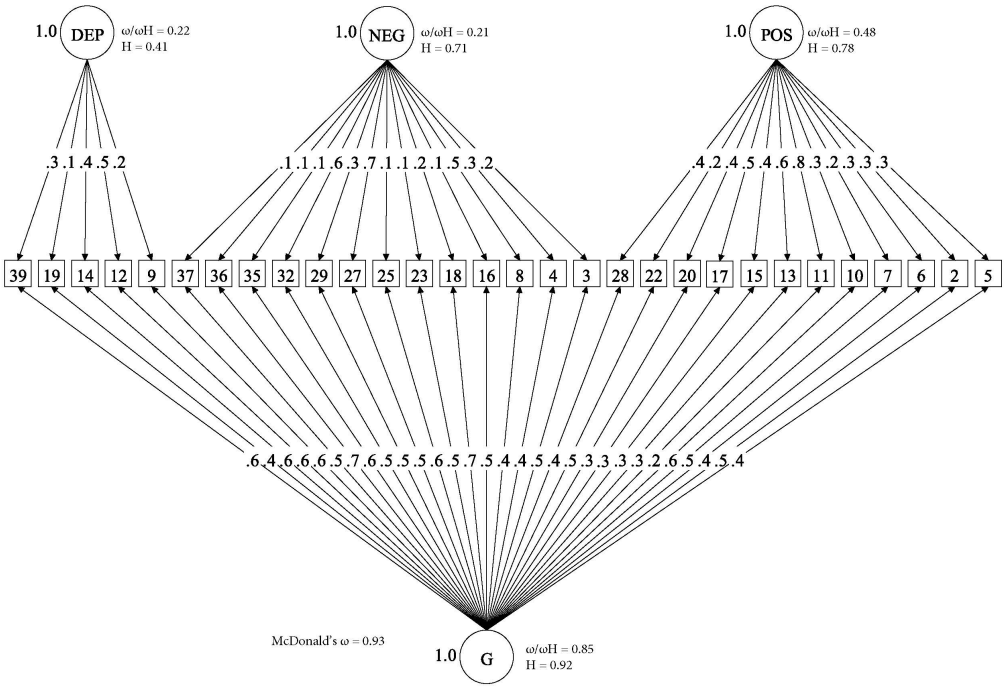


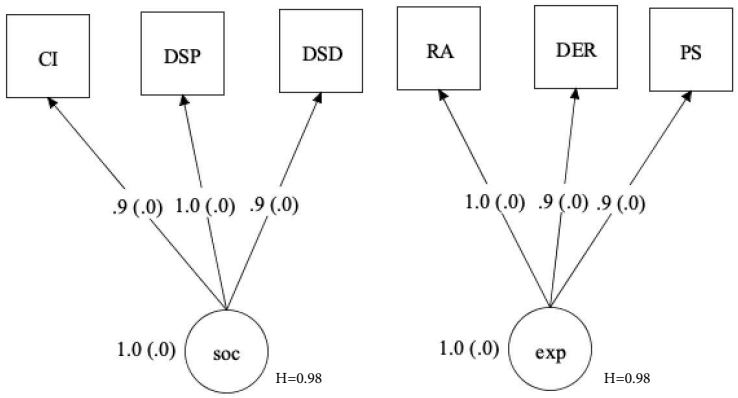
Figure S2 - Bifactor model of psychotic experiences in population controls based on CAPE items (2)



Explanatory note: Multidimensional model of negative symptoms

SDS was administered in all EU-GEI study sites with the exception of Verona, which was therefore excluded from SDS factor analysis and subsequent analysis on PRSs and negative symptoms. Item response modelling showed that the six SDS items had strong factor loading into the social avolition and lack of emotional expressivity dimensions. This is illustrated by the high reliability index *H* (Figure S3) (3). We therefore retained the multidimensional model of SDS for the present analysis, using the score at the emotional expressivity dimension as a measure of NEG symptoms in FEP patients.

Figure S3 – Multidimensional model of primary negative symptoms at FEP based on SDS items



(□) Observed variables (SDS items); (○) Unobserved variables (latent factors); (→) standardized item loading estimation onto latent factors; soc, avolition factor (e.g., active social withdrawal); exp, emotional expressivity factor. SDS items: CI, curbing of interests; DSP, diminished sense of purpose; DSD, diminished social drive; RA, restricted affect; DER, diminished emotional range; PS, poverty of speech.

H=construct reliability index; *H* is an index of the quality of the measurement model based on the loading of SDS items into each dimension (3). Indices can range from 0 to 1, with values closer to 1 indicating a better construct reliability and replicability across studies.

Explanatory note: Population structure and PRSs calculation

Supplementary methods

We applied a two-step procedure to account for the multi-ethnic structure of the EU-GEI sample, as follows:

1) Determination of the fine population structure using iterative pruning

Unsupervised clustering based on iterative pruning of single nucleotide polymorphisms (SNPs) was used in R, using the 'IPCAPS' package (4), to capture the fine-scale population structure. This method involves repetitive splits based on multivariate Gaussian mixture modelling of principal components (PCs). Unlike admixture profiling procedures, we did not make assumptions on the population ancestry in our sample, so the algorithm freely assigned individuals to population on nested datasets until no further population substructure was identified, by regulating the fixation index (F_{ST}) at 0.008, which is the common measure of the genetic distance between populations (4).

1b) Computation of cluster-specific principal components and PRSs

Genotype pre-processing steps were repeated for each identified population cluster, based on the assumption that allele frequencies vary across populations. Specifically, using plink 1.9, in each sub-population we excluded SNPs with minor allele frequency (MAF) <0.05%, Hardy Weinberg Equilibrium $p<10^{-6}$, missingness >2%, and subjects with heterozygosity F_{het} >0.14 or <-0.11 or relatedness >0.1. Within each population cluster, we built ancestry principal components and SZ and BP PRSs, with the aim to examine the predictive value of cluster-specific PRS and identify the suitable main sample for subsequent analysis.

2) Computation of main principal components and PRSs across populations

For constructing main PCs in the final sample, we pre-processed SNPs by using clumping which retains the *'index'* SNP for each linkage disequilibrium (LD) region (i.e., the SNP with the highest MAF), using the R packages 'bigsnpr' and 'bigstatsr' (5). Further, LD pattern differs by population, due to biological events such as, for example, inversion polymorphism (6). Thus, to ensure that main PCs did not capture mostly the variance due to differences in long-range genome regions with complex LD patterns, we ran an iterative algorithm to identify and remove these regions within our sample, using the (5).

Finally, we repeated the PRSice procedure in the main sample and constructed SZ-PRS, BP-PRS, SZ & BP- PRS, and SZ *v.* BP- PRS, using PGC GWAS as training sets (7-9).

Given that, in this sample, controls are representative of the general population and they are not matched with cases, two sensitivity analyses were performed to verify that case-control PRS prediction was not affected by differences in case-control ancestry distribution. First cases and controls were plotted in the PCA multidimensional space, within and across population nodes, in order to exclude systematic differences in their distribution at the visual inspection. Second, controls were formally matched with cases by sex and age-range within population nodes, in order to perform SZ-PRS case-control prediction in a final matched case-control sample.

Supplementary results

Sample and Genotype Quality Control (QC)

We recruited 1,130 FEP case participants and 1,497 control participants, who were assessed face-to-face. We successfully genotyped 72.7% of FEP (*N*=822, source of sample: 85.6% blood and 14.4% saliva) and 78.4% of controls (*N*=1,174, source of sample: 84.7% blood and 15.3% saliva). After imputation, 8,277,535 variants with info score > 0.6 were identified. Genotyped individuals were more likely to be older and of a white ethnicity than those not genotyped. Buccal sample collection was used more frequently in older individuals or in those of a black/mixed ethnicity (Table S1 and S2 - supplement).

Population structure

Iterative pruning led to the identification of three first-degree nodes (nodes 1-3; Figure S4). Node1 had three second-degree sub-nodes (A, B, C), comprising White-British individuals recruited in the UK and Dutch individuals recruited in Holland (A); Spanish individuals recruited in Spain (B), and Italian individuals recruited in Italy (C).

From node no.2 originated two main sub-nodes (sub-node D and E). Sub-node D was composed of White Brazilian ethnicity, with a smaller representation of Brown

Brazilian ethnicity, recruited in Brazil; whereas sub-node E was composed of individuals of Arab/Maghreb ethnicity recruited especially in France. As sub-node E was relatively small, we merged it with sub-node D.
From node no.3 two second-degree sub-nodes (sub-node F and G) originated. Sub-node F was most composed of Asian and South American individuals recruited across different countries, and Surinamese individuals recruited in Holland. Sub-node F was composed mainly of Black African, Black Caribbean, and Brown or Black Brazilian individuals, most recruited in the UK or Brazil.
At P_T=0.05, SZ-PRS was associated with case status in 5 out of 6 population clusters (sub-nodes A-F), explaining up to 13% of the variance (in sub-node D). Moreover, BP-PRS was associated with case status in 3 out of 6 population clusters (sub-nodes A, B, D), explaining consistently less variance than SZ-PRS.

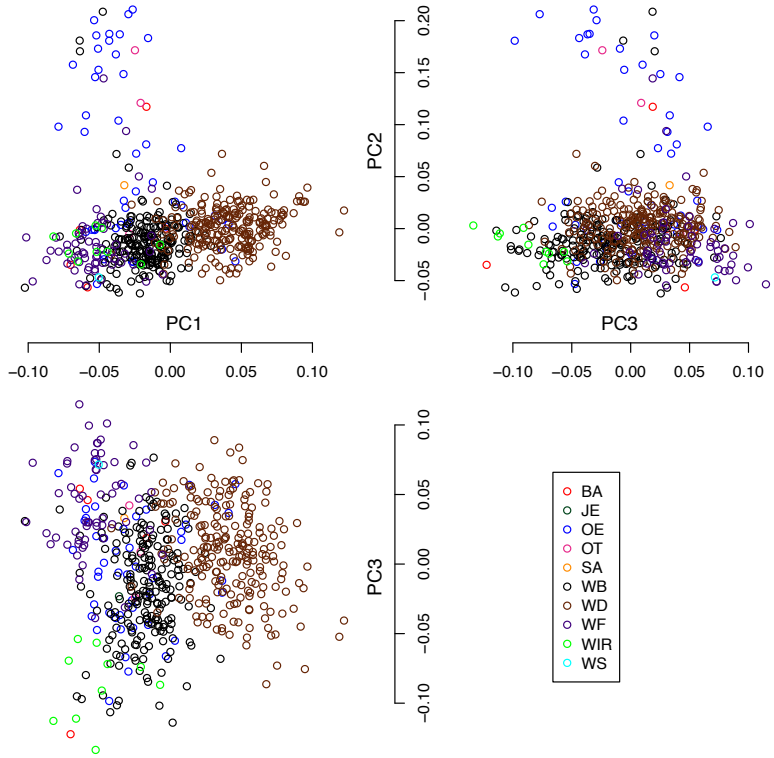
Sensitivity analyses excluded that the ancestry distribution of cases and controls in this sample could have a substantial impact on PRS prediction.
More specifically, first, there were no observable systematic differences in the case-control distribution in the PCA ancestry multidimensional spaces (Figure S5).
Second, SZ-PRS case-control prediction in the final matched sample, composed of =521 pairs of cases and controls (N=179 from sub-node A; N= 113 from sub-node B; N=106 from sub-node C; and N=123 from sub-node D), accounted for a Nagelkerke's R2 of 0.094 (p=8.4x10-17) at the fixed Pt-threshold of 0.05. These results were similar to the main analysis in 621 cases and 982 unmatched controls (Nagelkerke's R2 = 0.09; p=6.9x10-26), at the same fixed Pt-threshold of 0.05.

Main PCs and PRS computation
Based on the case-control discriminative value of SZ- and BP-PRS, we merged 1,677 individuals clustered in nodes from A-E in SZ-PRS analysis; and we further excluded nodes C and E in BP-PRS analysis.
Five long-range LD regions on chromosome 6 (from 29155749 to 30578335; from 31386313 to 31978687; from 32804798 to 33460609; from 33841361 to 34455330; from 35377301 to 36288879) and one long-range LD region on chromosome 8 (from 15773120 to 19548644), were identified in the main sample and removed for computing the main PCs.

Figure S4 – Identified population subgroups and related SZ-PRS and BP-PRS

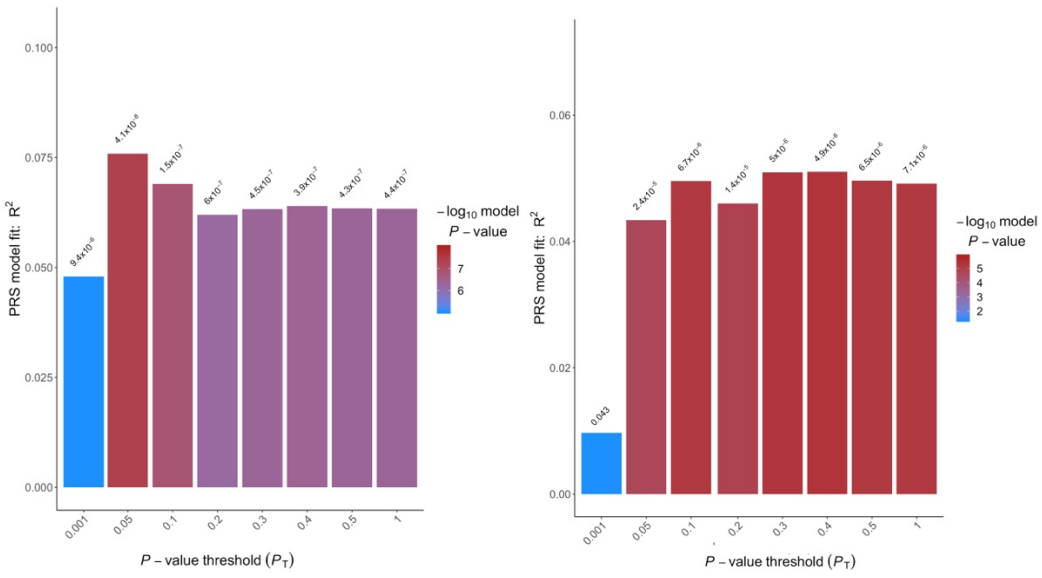
For each population cluster (aka node), three plots are presented. Plots A to F show three ancestry principal components for each individual coloured by their self-reported ethnicity. Plots A1 to F1, and A2 to F2, show the variance in case-control status (y-axis) explained by SZ-PRS and BP-PRS respectively, at different P_T (x-axis). The gradient of colour of the bars represent the significance of the association (i.e. the redder, the more significant the association is); a fixed P_T =0.05 was however *a priori* selected. All the abbreviation is reported at the end of the supplementary material.

A) NODE no.1 Sub-node A (most represented population: 40% White-Dutch (WD) recruited in Holland; 38% White-British (WB) recruited in UK; 11% White-French (WF) recruited in France)

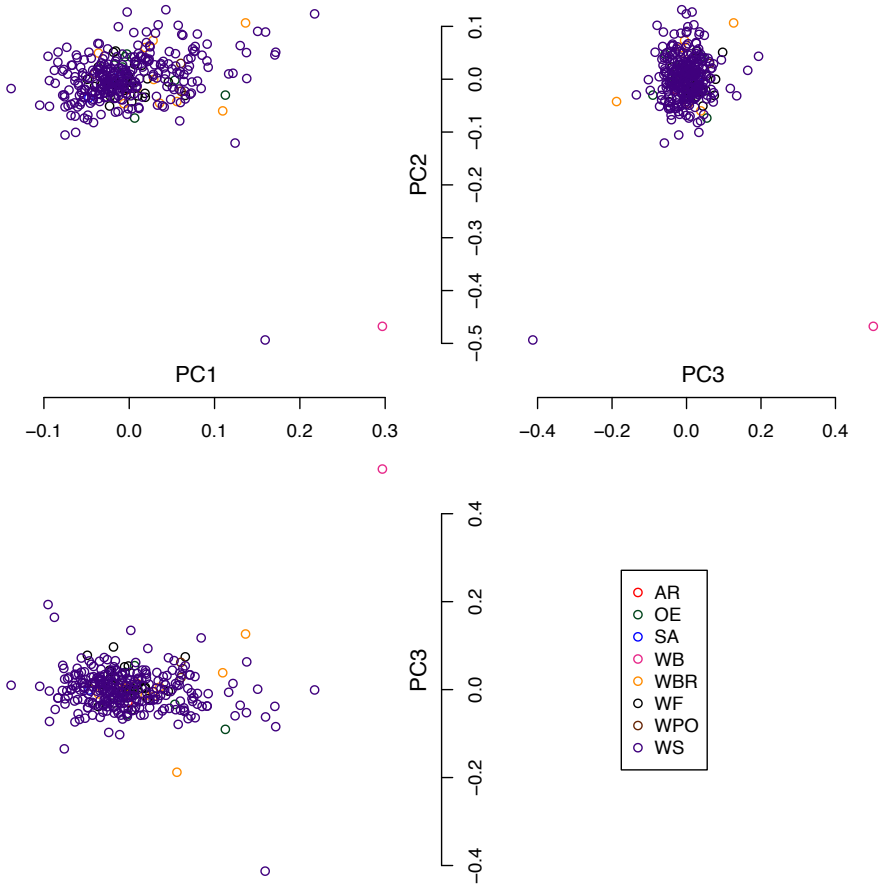


A1) SZ-PRS, at Pt=0.05: Nagelkerke's R^2=0.076; p=4.1x10^{-8}

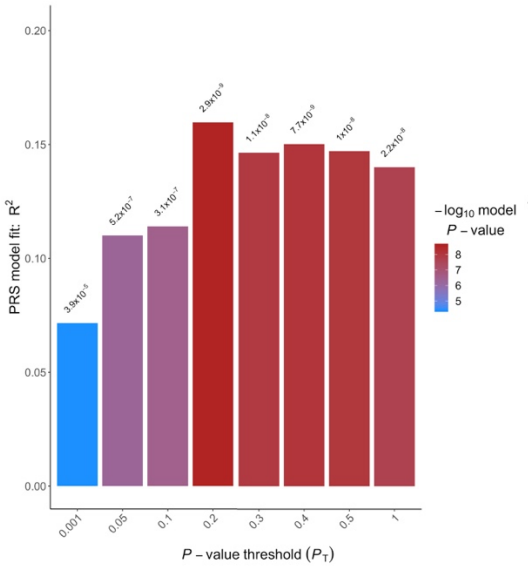
A2) BP-PRS, at Pt=0.05: Nagelkerke's R^2=0.043; p=2.4x10^{-5}



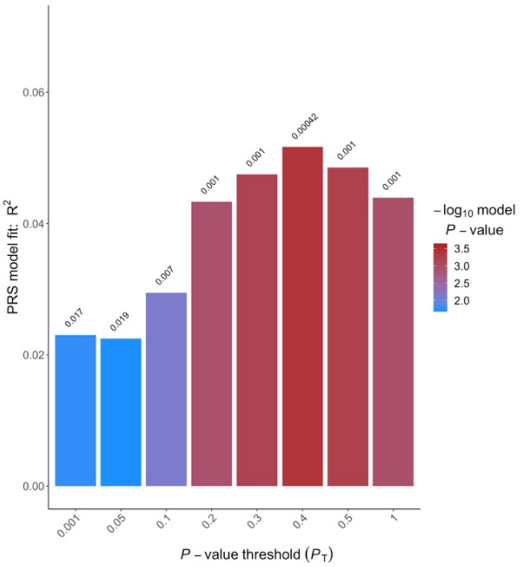
B) Sub-node B (most represented population: 84% White-Spanish (WS) recruited in Spain; 8% White-French (WF) recruited in France; 2% White-Brazilian (WB) recruited in Brazil)



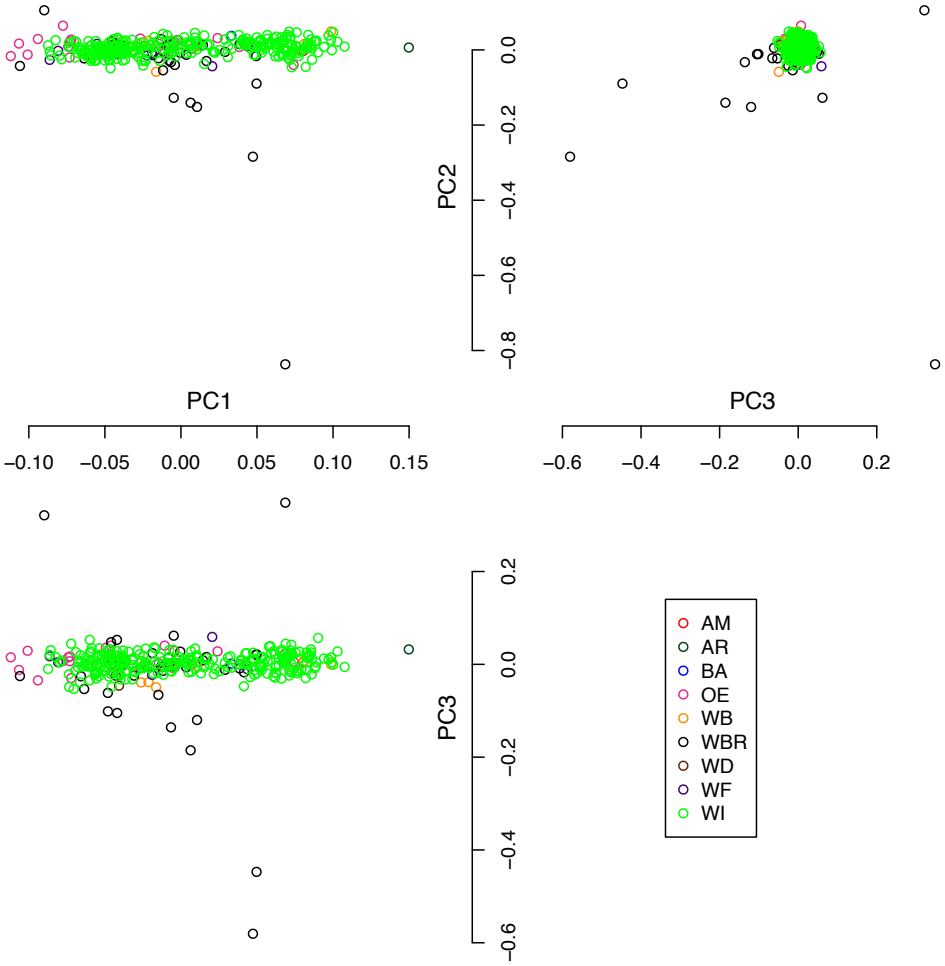
B2) SZ-PRS: at Pt=0.05, Nagelkerke's R^2=0.11; p=5.2x10^{-7}



B2) BP-PRS:at Pt=0.05, Nagelkerke's R^2=0.022; p=0.019

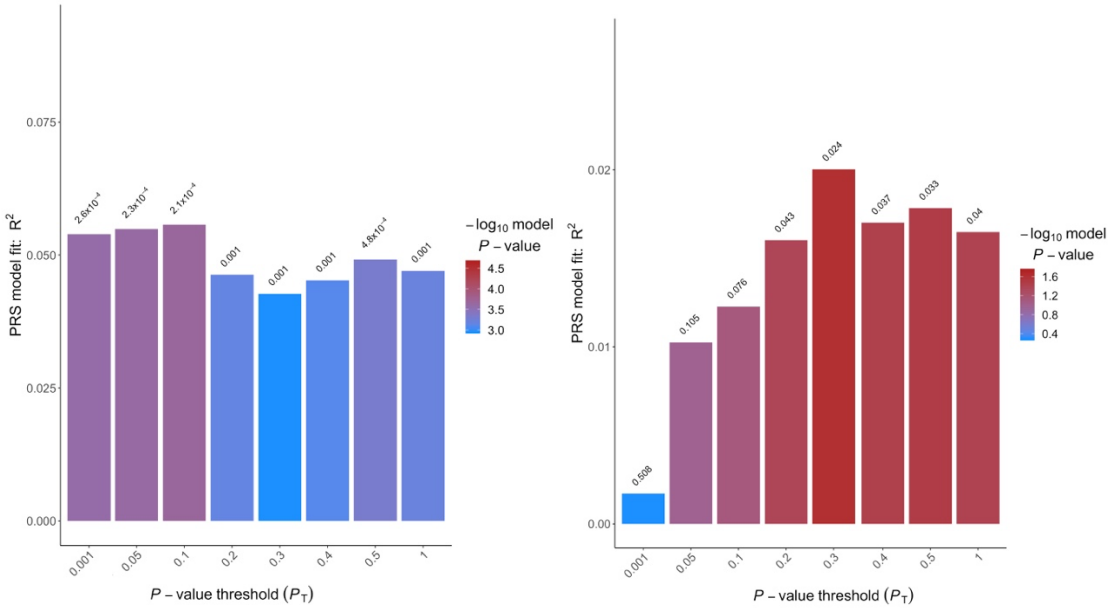


C) Sub-node C (most represented population: 77% White-Italian WI) recruited in Italy; 11% White-Brazilian (WBR) recruited in Brazil; 3% White-French (WF) recruited in France)



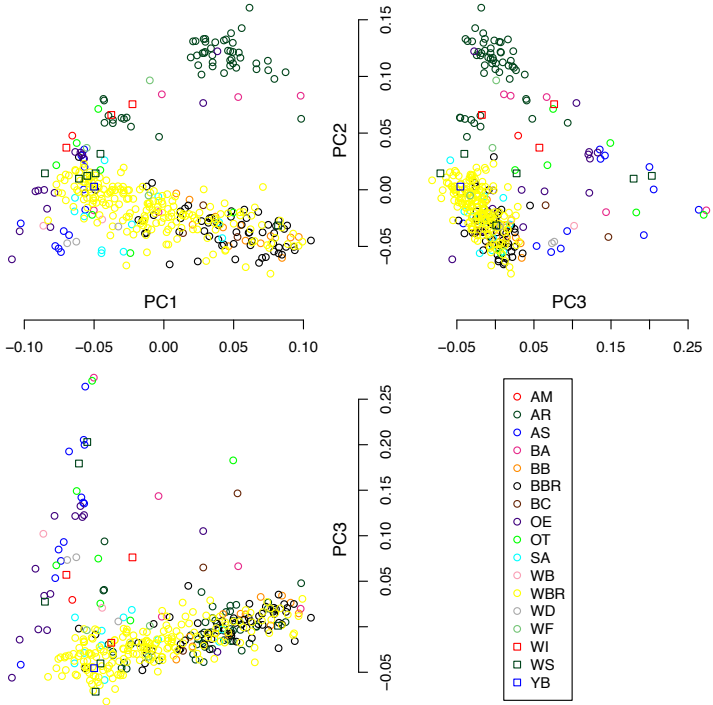
C1) SZ-PRS - at Pt=0.05, Nagelkerke's R^2=0.052; p=2.3x10^{-4}

C2) BP-PRS - at Pt=0.05, Nagelkerke's R^2=0.01; p=0.105

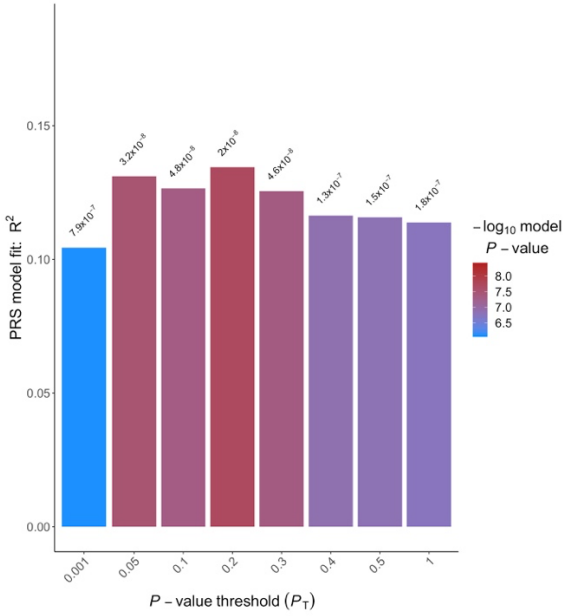


Node no.2

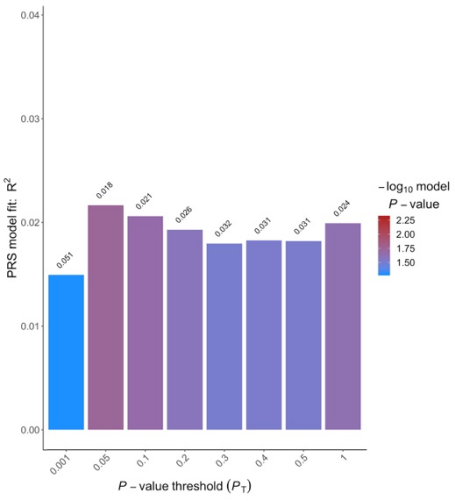
D) Sub-node D (most represented population: 49% White-Brazilian recruited in Brazil; 16% Brown-Brazilian recruited in Brazil; 7% Arab/Maghreb recruited in France)



D1) SZ-PRS - at Pt=0.05, R^2=0.131; p=$3.2x10^{-8}$

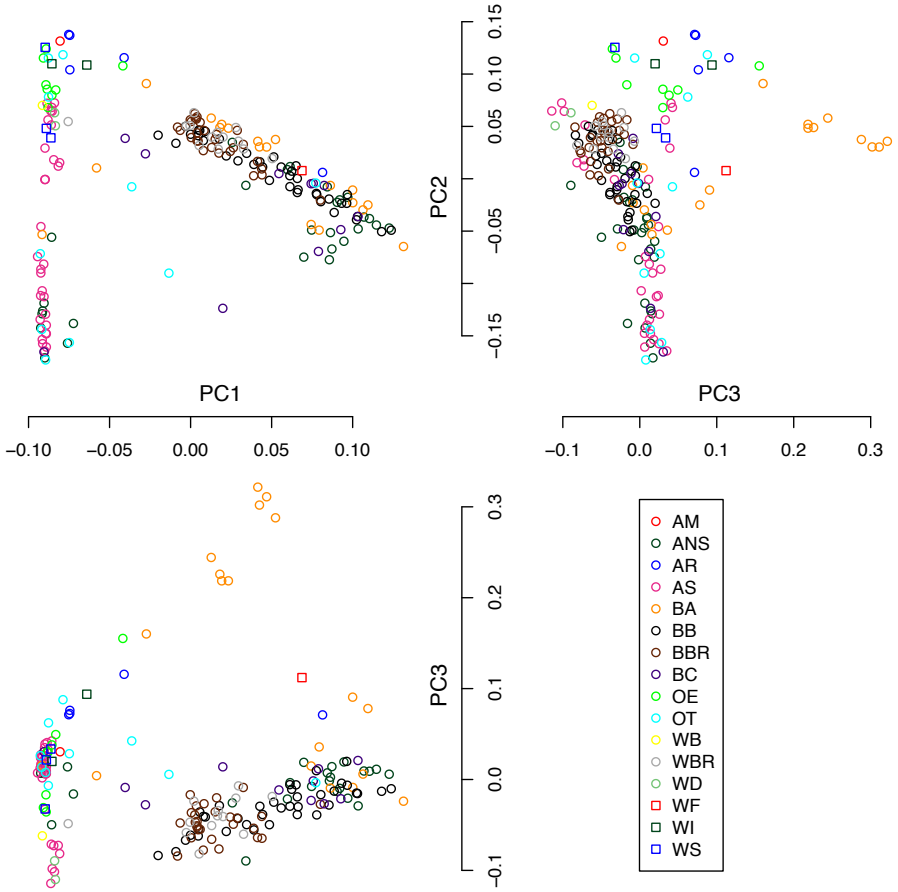


D2) BP-PRS - at Pt=0.05, R^2=0.021; p=0.018

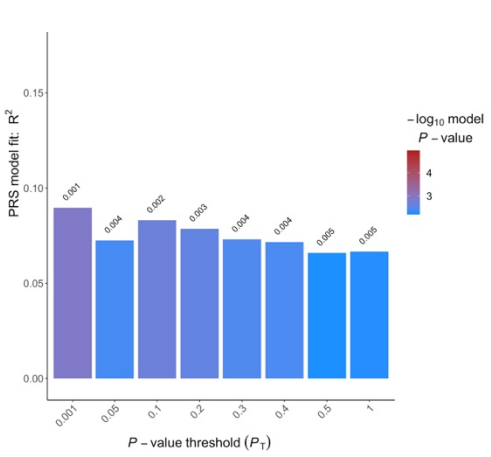


Node no.3

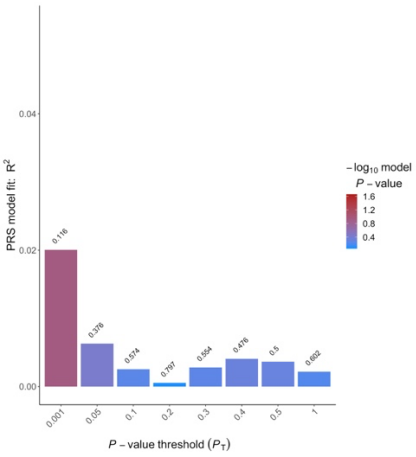
E) Node E (most represented population Asian recruited in UK or Holland, Indian recruited in UK, American and South Americans recruited in Spain, Surinamese recruited in Holland, mixed White-Black Caribbean recruited in UK)



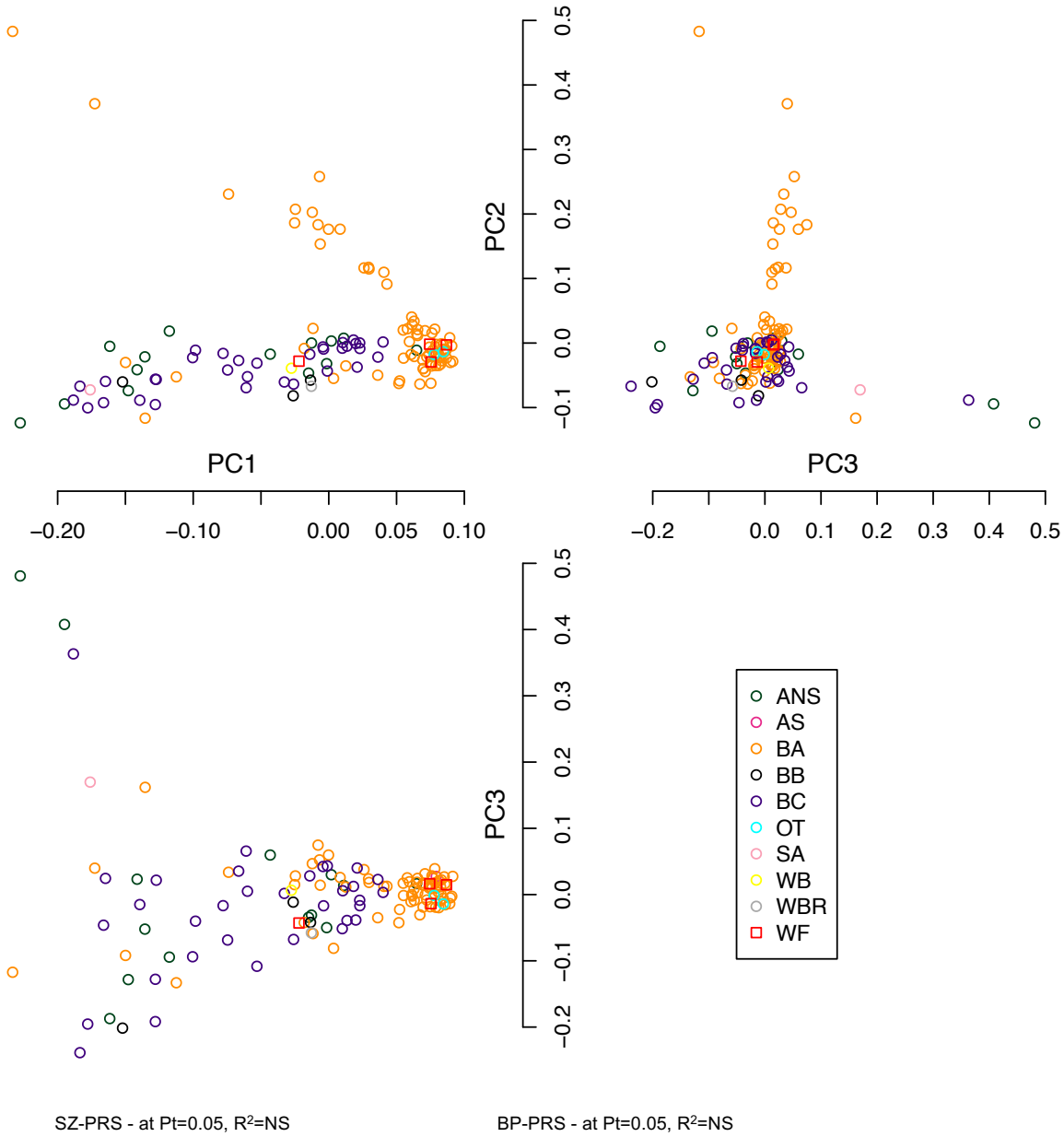
E1) SZ-PRS - at Pt=0.05, R^2=0.06; p=0.004



E2) BP-PRS - at Pt=0.05, R^2=0.01; p=0.376



Node F (most represented population Black African and Black Caribbean recruited in the UK)



SZ-PRS - at Pt=0.05, R^2=NS

BP-PRS - at Pt=0.05, R^2=NS

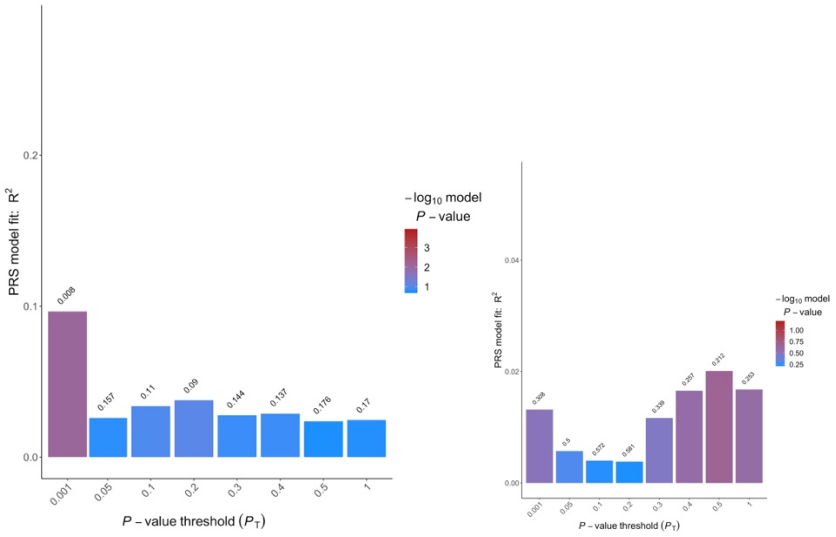
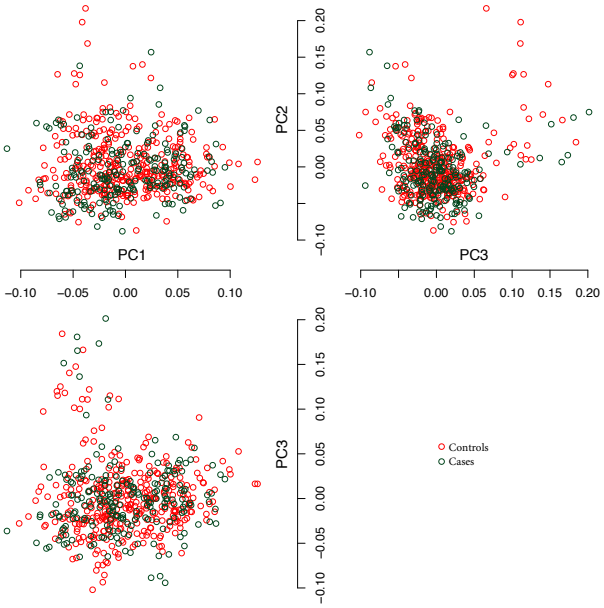
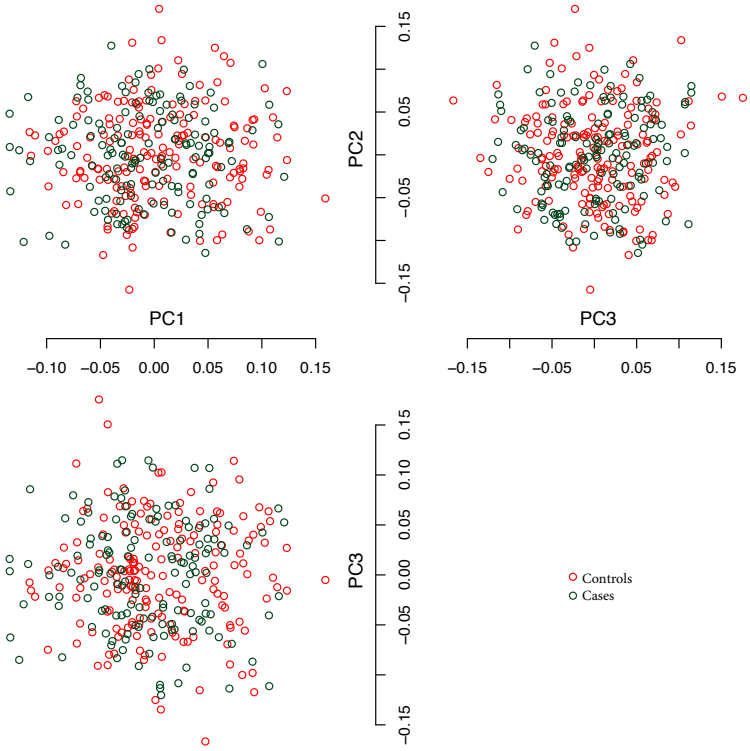


Figure S5 – Cases and controls distribution across population subgroups
The plots show no observable systematic differences in the PCA ancestry distribution between cases and controls in population sub-nodes of interest (i.e., ‘sub-node A’, mostly composed of British and Dutch individuals; ‘sub-node B’, mostly composed of Spanish individuals; ‘sub-node C’, mostly composed of Italian individuals; ‘sub-node D’, mostly composed of Brasilian individuals) and in the final merged dataset.

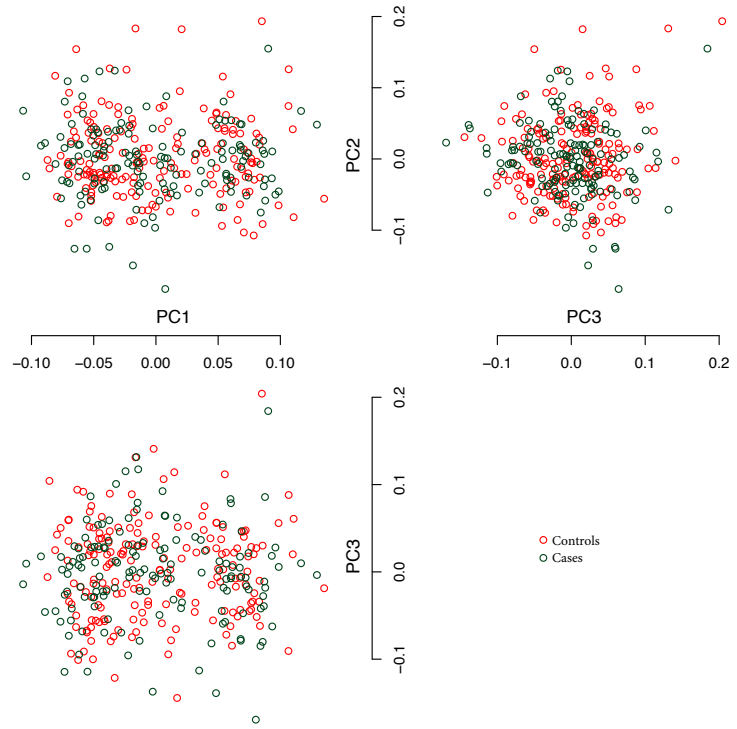
Sub-node A



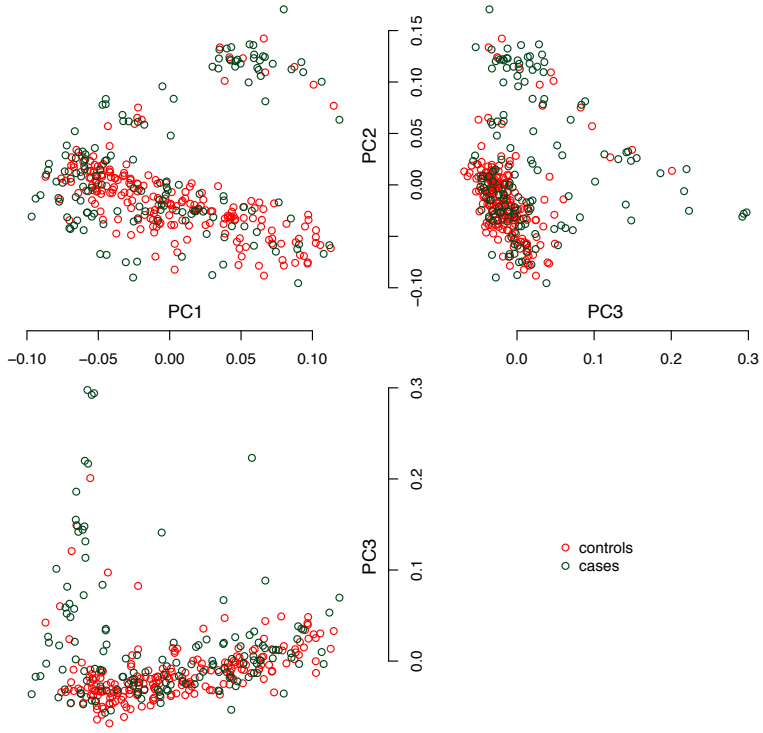
Sub-node B



Sub-node C



Sub-node D



Final sample (subnodes A, B, C, and D)

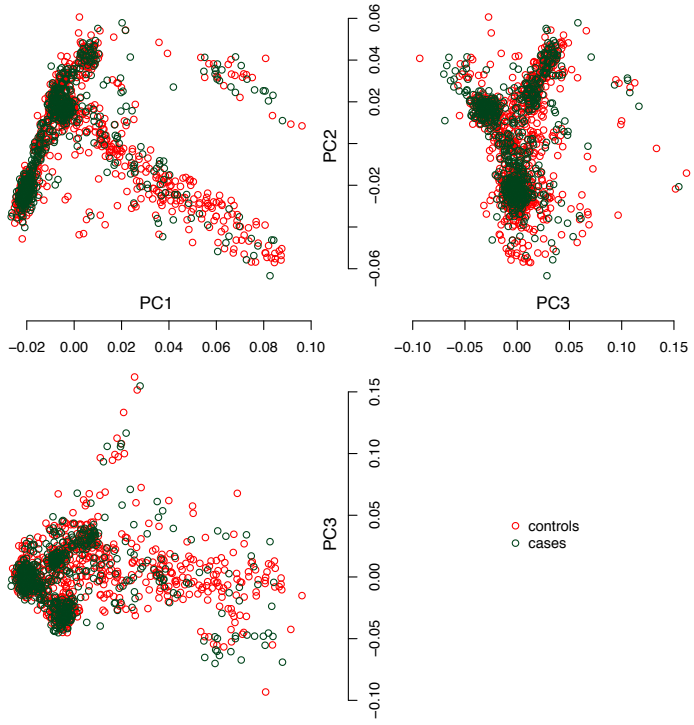
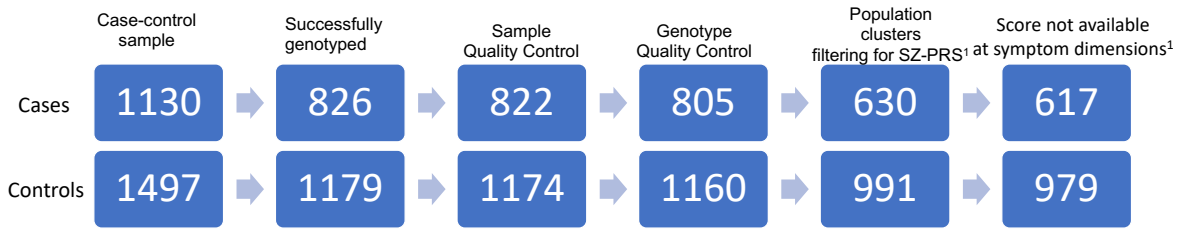
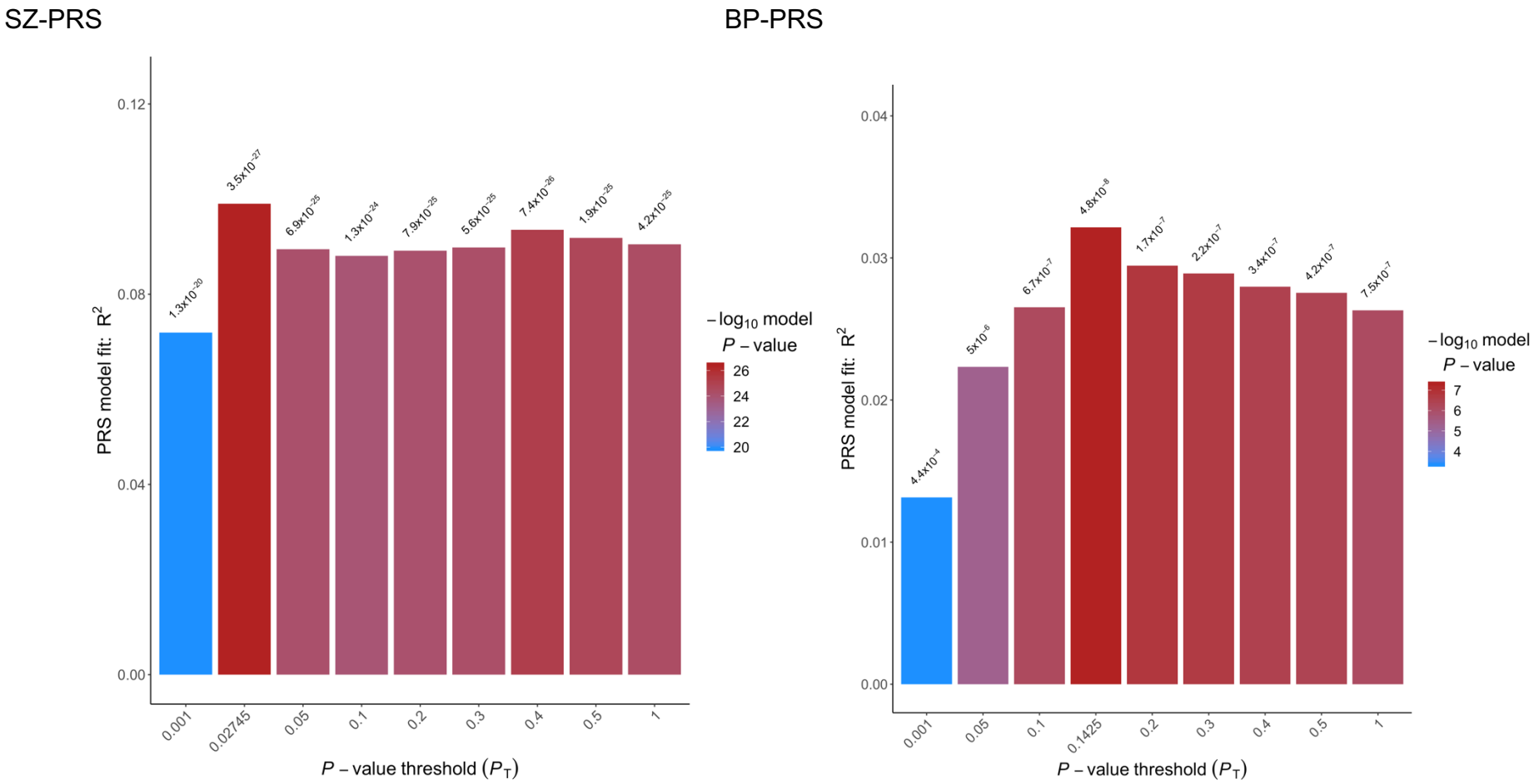


Figure S6 - Flow chart to the final analysed sample



[1]For the examination of BP-PRS symptoms, case sample was further reduced from to 518 subjects (505 with symptom dimension score available)

Figure S7 – SZ-PRS and BP-PRS in the final sample at different Pt-thresholds

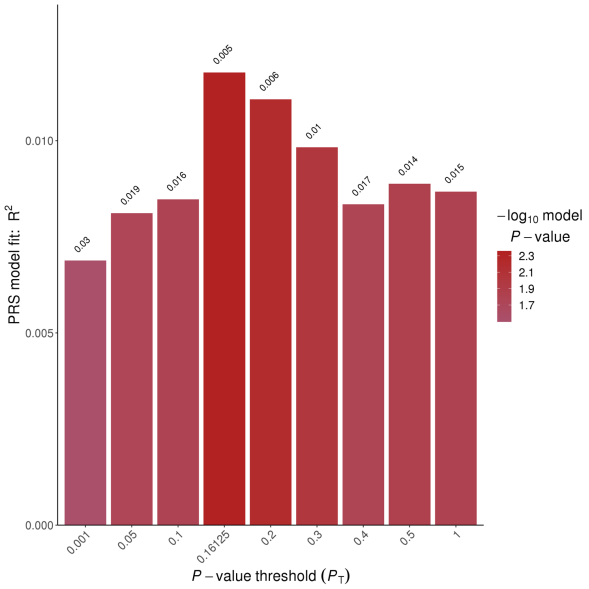


Explanatory note: The plots shows the variance in case-control status (y-axis) explained by SZ-PRS at different P_T (max no. of variants after clumping at P_T=1: 106,508; no. of variants at predefined P_T=0.05: 26,281); and by BP-PRS at different P_T (max no. of risk variants after clumping at PT=1: 88,084; no. of risk variants at predefined PT=0.05:18,092)

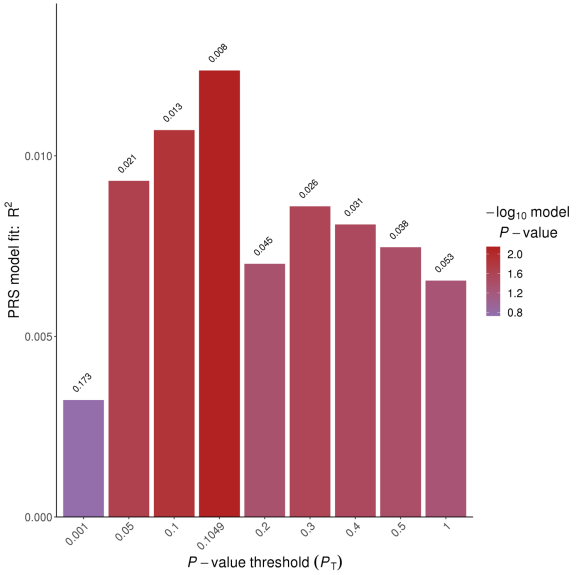
Figure S8 – SZ-PRS by POS and NEG in patients and controls

The plots show the variance in POS / NEG symptom / experience dimension scores (y-axis) explained by SZ-PRS at different P_T (max no. of risk variants after clumping at P_T=1: 106,508; no. of risk variants at predefined P_T=0.05: 26,281). All the associations remained significant after permutation analysis.

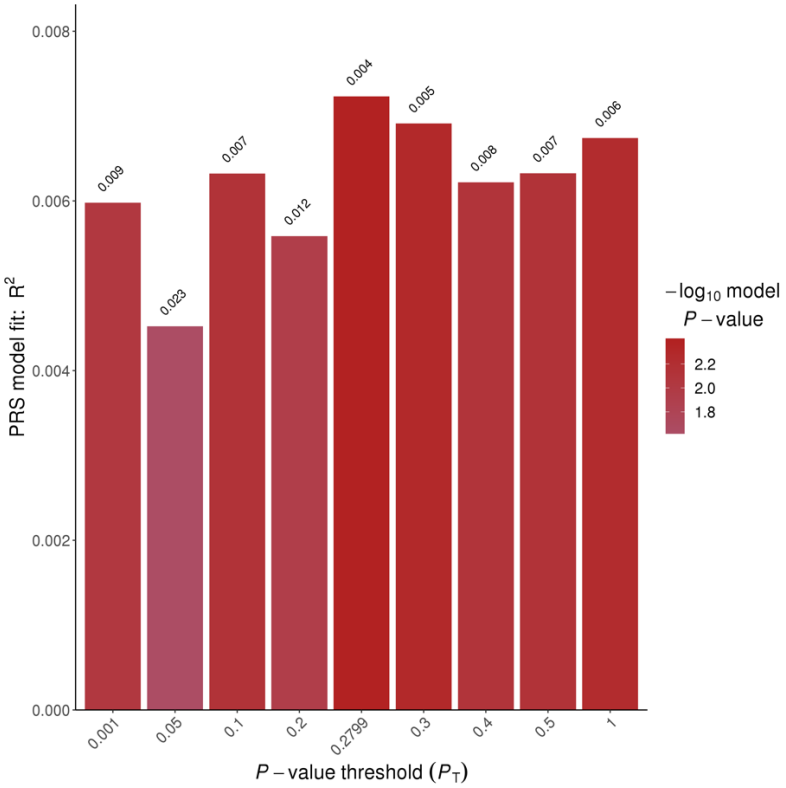
SZ-PRS and POS symptoms in cases



SZ-PRS and NEG symptoms in cases



SZ-PRS and POS psychotic experiences in controls



SZ-PRS and NEG psychotic experiences in controls

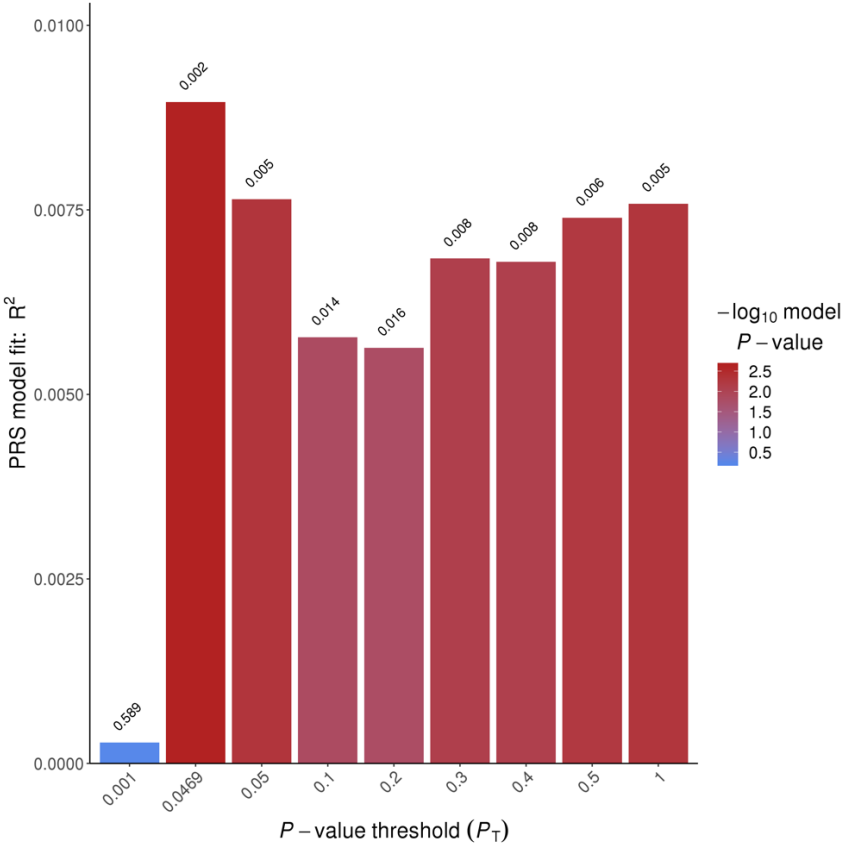


Table S3 – Self-reported ethnicity of cases and controls in the final sample for each population - cluster

Subnode A

Self-reported Ethnicity	Freq.	Percent	Cum.
BA (Black African)	5	0.88	0.88
JE	1	0.18	1.06
OE	48	8.50	9.56
OT	2	0.35	9.91
SA	1	0.18	10.09
WB	211	37.35	47.43
WD	225	39.82	87.26
WF	61	10.80	98.05
WIR	10	1.77	99.82
WS	1	0.18	100.00
Total	565	100.00	

Subnode B

Self-reported Ethnicity	Freq.	Percent	Cum.
AR	1	0.30	0.30
OE	9	2.73	3.03
SA	2	0.61	3.64
WB	1	0.30	3.94
WBR	12	3.64	7.58
WF	26	7.88	15.45
WPO	2	0.61	16.06
WS	277	83.94	100.00
Total	330	100.00	

Subnode C

Self-reported Ethnicity	Freq.	Percent	Cum.
AM	1	0.29	0.29

AR	1	0.29	0.58
BA	1	0.29	0.88
OE	25	7.31	8.19
WB	6	1.75	9.94
WBR	39	11.40	21.35
WD	1	0.29	21.64
WF	7	2.05	23.68
WI	261	76.32	100.00
Total	342	100.00	

Subnode D

Self-reported Ethnicity	Freq.	Percent	Cum.
AM	1	0.27	0.27
AR	50	13.33	13.60
AS	12	3.20	16.80
BA	5	1.33	18.13
BB	12	3.20	21.33
BBR	58	15.47	36.80
BC	2	0.53	37.33
OE	13	3.47	40.80
OT	7	1.87	42.67
SA	11	2.93	45.60
WB	2	0.53	46.13
WBR	187	49.87	96.00
WD	3	0.80	96.80
WF	3	0.80	97.60
WI	3	0.80	98.40
WS	5	1.33	99.73
YB	1	0.27	100.00
Total	375	100.00	

Abbreviation:

AM American

ANS Antillean/Surinamese

AR Arab/Maghreb

AS Asian

BA Black African

BB Black Brazilian

BBR Brown Brazilian

BC Black Caribbean

JE Jewish - Other European

OE Other European

OT Other Mixed

SA South American

WB White British

WBR White Brazilian

WD White Dutch

WF White French

WI White Italian

WIR White Irish

WPO White Portugal

WS White Spanish

YB Yellow Brazilian

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Chapter 7: General Discussion

7.1 Summary of the aims

The overall aim of this thesis was to examine the latent structure of psychopathology at FEP, and the relationship of derived transdiagnostic symptom dimensions with biological and environmental factors.

The first part of this thesis has examined different models of psychopathology pertaining to the psychosis spectrum. The first hypothesis explores whether one general factor contains traits shared among categories of non-affective and affective psychotic disorders, and five specific dimensions contain distinctive traits across these categories (Chapter 4). This structure is statistically reflected through the bifactor model of psychopathology, which challenges the unsatisfactory traditional distinction between categories of non-affective and affective psychosis. Only a few studies have proposed a bifactor solution to solve dimensionality issues in psychosis, and no studies to date have constructed this model at the onset of psychosis, where symptoms are less likely to be confounded by prolonged treatments and social stigma. Hence, I have applied bifactor modelling to psychosis symptoms using a multi-site incidence sample of FEP patients; moreover, I have replicated the bifactor structure of psychopathology in controls representative of the population at risk for psychosis in each study site (Chapter 5). I have evaluated the psychometric properties of the bifactor model, including reliability and strength indices, and compared the bifactor model with competitive unidimensional and multidimensional solutions.

However, the validity of the bifactor solution cannot rely on psychometric data only. The plausibility of alternative phenotypes in psychosis should be tested by its coherence with external factors, in the context of a falsifiable integrated theory (Kendler, 2015). Thus, the second part of this thesis aimed to examine the relationship of the bifactor latent psychopathology structure with external factors. The general assumption was that the continuous distribution of symptoms reflected the gradient of neurodevelopmental impairment in psychosis and the exposure to socioenvironmental risk factors such as use of cannabis. I have investigated these aspects in different studies (Chapters 4, 5, and 6), under the hypothesis that individuals may follow different pathways to psychosis, depending on the source and timing of neurodevelopmental aberrances (Murray *et al.*, 2017a).

In addition to validating the latent factors of psychopathology, the third part of this thesis has disentangled the relationship between cannabis use and psychotic symptoms, with the aim to inform clinical practice and research in this field (Chapter 5). The recent increase in accessibility of high-potency cannabis in Europe (Freeman *et al.*, 2019) demonstrates the importance of this investigation and in particular the need to develop strategies that prevent cannabis use. Given that daily use of high potency cannabis has been associated with a higher incidence of psychotic disorders across Europe (Di Forti *et al.*, 2019a), I have hypothesised that this pattern of use would further be associated with the highest positive symptom dimension score. Moreover, I have hypothesised that the symptom dimension profile in cannabis-associated psychosis would reflect the lack of an early neurodevelopmental impairment, given that the use of cannabis may impact on a late stage of brain maturation, i.e. during adolescence (Bloomfield *et al.*, 2016). In particular, the existence of a specific cannabis-associated psychopathology, differing

from other forms of psychosis, would be suggestive of a cannabis-specific pathogenic trajectory, and it would reinforce the evidence that cannabis use is a component cause of psychosis (Murray and Di Forti, 2016). Moreover, these findings would serve as the basis for developing personalised treatment and care algorithms for clinicians.

The fourth part of this thesis has further validated the latent structure of psychosis using genetic data (Chapter 6). The study aimed to determine whether common genetic variants conferring psychosis risk were also acting as 'modifier' factors of psychosis expression. In the literature, studies using larger samples reported that SZ-PRS indexed negative symptomatology in chronic schizophrenia samples (Fanous *et al.*, 2012, Bipolar Disorder Schizophrenia Working Group of the Psychiatric Genomics Consortium and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018, Jonas *et al.*, 2019). However, the novelty of my study is the use of a bifactor model examining psychopathology in FEP patients, as well as recruiting controls representative of the population living in the boroughs where all new cases of psychosis were identified in the time-period of the study. The use of a FEP sample is crucial for examining 'primary' negative symptoms (Peralta *et al.*, 2000), given that, in subsequent stages of the disorder, the pattern of symptoms can be more severely confounded by non-genetic factors, such as enduring antipsychotic treatment (Kirschner *et al.*, 2017) and the loss of social status that may result from the stigma of a psychosis diagnosis (Birchwood *et al.*, 2007). Finally, my study has served to examine for the first time the combined effect of cannabis use and SZ-PRS on symptom dimensions, under the hypothesis that these are two independent factors affecting symptom presentation.

7.2 Key findings

Psychopathology structure at FEP

In Chapter 4, I showed that a bifactor model, composed of one general factor and five specific dimensions of positive, negative, disorganisation, manic, and depressive symptoms, best represents psychopathology at FEP when compared with competitive theory-based models. These results challenge, from a psychometric perspective, the neat Kraepelin dichotomy between non-affective and affective psychotic disorders. Specifically, they indicate that the formation of specific dimensions is justified in addition to the general factor, and vice versa, across diagnostic categories.

Furthermore, in Chapter 5, I replicated the bifactor structure of psychopathology in population controls, whereby psychotic experiences were best represented by one general factor and three specific dimensions.

Altogether, these results are in line with the notion that the psychotic symptom distribution follows a continuum in the general population (van Os *et al.*, 2009) as well as in patients across diagnostic categories of psychotic disorders (Allardyce *et al.*, 2007b).

Symptom dimensions by demographic and context factors

My results in Chapter 4 show that demographic and context factors map onto the general and specific symptom dimensions. Transdiagnostic negative symptoms at FEP were more expressed in men and associated with an earlier age at psychosis onset; according to a neurodevelopmental model of psychosis, negative symptoms,

being male, and having an early age at onset are all suggestive of early neurodevelopmental impairment in psychosis (Castle and Murray, 1991).

Transdiagnostic positive symptoms at FEP were more expressed in ethnic minorities, coherent with the literature showing, in these groups, higher incidence of subclinical and frank psychosis (Sharpley *et al.*, 2001, Fearon *et al.*, 2006, van Os *et al.*, 2009).

Transdiagnostic depressive symptoms at FEP were more expressed in women and associated with a late age at onset, which is consistent with what is known about neurodevelopmental-related gender differences in psychosis (Castle and Murray, 1991, Abel *et al.*, 2010).

Finally, the urban environment was associated with a higher score on the general psychosis factor, consistently with the notion that the urban context may involve exposure to various risk factors and result in heterogenous psychopathology outcomes (van Os *et al.*, 2002b).

Overall, these findings can be interpreted according to a developmental risk model of psychosis, where an early neurodevelopmental pathway indexed by prominent negative symptoms can be discerned from an affective pathway(Murray *et al.*, 2004). Moreover, a risk pathway involving substance use is presented in the following paragraph.

Symptom dimensions by cannabis use

Study 2 established a dose response relationship between the score at the positive symptom dimension at FEP and the extent of lifetime exposure to cannabis; moreover, it showed a higher score at the negative symptom dimension at FEP in individuals who never tried cannabis (Chapter 5). The existence of a particular

symptom profile of cannabis-associated psychosis is coherent with the hypothesis of a disease trajectory characterised by less early neurodevelopmental impairment, since the use of high potency cannabis might produce disturbances in a late stage of neurodevelopment, in adolescence (Di Forti *et al.*, 2014, Murray *et al.*, 2017b).
The study also showed that in controls, the positive psychotic experience dimension was associated with a recent use but not with the extent of lifetime use of cannabis. This is in line with evidence suggesting that individuals vary in their susceptibility to long-lasting effects of cannabis (Hurd *et al.*, 2019).

Symptom dimensions by polygenic risk scores

Findings from study 3 indicated in patients that SZ-PRS was associated with higher scores on both the positive and negative symptom dimensions (Chapter 6).
As introduced earlier, the association between SZ-PRS and the negative symptom dimension was previously shown in larger studies of chronic patients (Fanous *et al.*, 2012, Ruderfer *et al.*, 2014, Bipolar Disorder Schizophrenia Working Group of the Psychiatric Genomics Consortium and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018, Jonas *et al.*, 2019), whereas the association between SZ-PRS and the positive symptom dimensions is novel and warrants cautiousness in its interpretation. Indeed, a limitation of previous studies is that positive symptoms may be attenuated, and negative symptoms may deteriorate through the prolonged use of antipsychotics. Hence, although pending replication in larger FEP samples, my findings show 1) an association between SZ-PRS and the positive symptom dimension at FEP, and that 2) the association between SZ-PRS and the negative symptoms holds even when the evaluation is restricted to primary as opposed to secondary negative symptoms. This observation is coherent with twin

and adoption studies showing that negative symptoms are the most heritable schizophrenia trait (Cardno *et al.*, 2008). Furthermore, contrary to the initial hypothesis, study 3 has reported no evidence that a general psychosis factor at FEP indexes a common genetic propensity to develop schizophrenia and bipolar disorder, which suggests further research is needed to validate the use of a general factors as a phenotype in psychotic disorders, for example examining a larger set of pleiotropic genes (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Finally, my findings show that SZ-PRS is associated with either general and positive, negative, and depressive psychotic experience dimensions in population controls, which is consistent with the notion of a continuum of psychosis in the general population (van Os *et al.*, 2009), and with the evidence of the genetic correlation of psychotic experiences with multiple psychiatric disorders (Legge *et al.*, 2019b).

7.3 Wider implications

7.3.1 Should we use symptom dimensions or categorical diagnoses?

Psychometric findings from the bifactor model of psychopathology provide new insights into symptom distribution in the general population (Chapter 5) and in FEP patients (Chapter 4), regardless of diagnostic categories.

Nevertheless, in clinical practice, setting categorical boundaries is instrumental in reducing clinical complexity and using disease-specific guidelines. Should we then discard the use of diagnostic categories in the field of psychosis, based on the lack of convergence of validators in clearly distinguishing non-affective from affective psychosis? Answering this question requires a brief digression into the field of epistemology. The categorisation approach in psychiatry is deductive, i.e. it follows a top-down logic in that we try to confirm a general theoretical construct (diagnosis)

based on a series of converging elements presented by the patient. Indeed, the use of the current nosological systems allows patients to be treated according to guidelines that reflect the evidence from studies based on these diagnoses. Given that, Eric Turkheimer introduced the adverbs ‘meaningful but arbitrary’ (MBA) to best describe the utility without validity of nosology constructs (Turkheimer *et al.*, 2008). In fact, a diagnosis of psychotic disorders involves two MBA distinctions: the first operates between ‘normality’ and the psychotic disorder, and the second between different classes of psychotic disorders.

Alternative to the categorisation approach is the symptom-based approach which is inductive in its exploratory stage. However, the statistical process of identifying latent factors (based on the joint co-variation of observed symptoms) is only apparently a data-driven process. A few MBA actions occur in any factor analysis and involve, for example, the decision to establish the joints within the multidimensional space. Indeed, any software addresses this indeterminacy problem by imposing a ‘simple structure’ (Thurstone, 1940), which allows each item to load highly onto no more than one factor. Moreover, the multidimensional space can be rotated in different ways to create a variety of simple structures, ranging from uncorrelated latent factors (e.g. orthogonal rotations) or correlated factors at different degrees and orders (e.g. oblique rotations). Leaving the multidimensional space undetermined would otherwise make data hardly interpretable, at least in the case of classic psychopathology. An example of a multidimensional structure without a simple structure is the Guttman’s intelligence radex (Guttman, 1954), where stimuli are plotted unrotated in circular dimensions. However, Guttman aimed to demonstrate that similarities in intelligence could be represented by a unique general intelligence factor, without being interested in setting joints within that space (Kendler *et al.*,

2017). Interestingly, Guttman's 'G' (i.e. 'General') factor of intelligence encouraged research into a general factor of psychopathology, as presented in the next paragraph.

In summary, psychometric findings from Chapter 4 of my thesis do not answer the question whether research into psychosis should be conducted using symptom dimensions or diagnostic categories. Indeed, both dimensions and categories are instrumental, hence choosing one of the two should primarily depend on individual research purposes (Zachar and Kendler, 2017). Rather, my findings are relevant as they re-affirm two points. First, even if continuously distributed symptom dimensions are more flexible constructs than rigid diagnostic categories, this approach carries a degree of indeterminacy - therefore any taxon interpretation should be avoided when based on symptoms only. Indeed, a factor analysis of symptoms is nothing more than an instrumental MBA operation that organises the multivariate space of psychopathology according to a psychometric model. Indeed, a debate in the philosophy of science concerns the fact that latent factors, as well as diagnostic categories, are instrumental constructs that do not exist in nature (Kendler, 2015). Hence, latent factors should be validated investigating the common causes associated with the co-variation of certain sub-groups of data (Kendler, 2015). Secondly, for symptom dimensions to serve as useful and valid psychosis phenotypes, it is necessary that their association with external factors is coherent with a solid theoretical framework, for example, an integrated developmental risk factor model of psychosis (Murray *et al.*, 2017a).

7.3.2 The research into a general factor of psychopathology

The application of bifactor modelling in an incidence psychosis sample (Chapter 4), allowed the emergence of a general factor unifying manic and delusional items at FEP, challenging Kraepelin's dichotomy. Moreover, a general factor emerged in population controls, encompassing a more heterogenous series of items, including positive, negative, and depressive psychotic experiences. Although the use of different scales and methods for rating psychotic symptoms and experiences do not allow a direct comparison, the qualitative differences in the general factor between FEP and controls were expected (Caspi *et al.*, 2014), under the notion that psychopathology expression would be less specific in the general population than in patients (Caspi and Moffitt, 2018, Legge *et al.*, 2019b).

My findings from the bifactor models question the existence of a general factor in psychosis (Lahey *et al.*, 2012, Reininghaus *et al.*, 2016, Caspi and Moffitt, 2018). Attempts to identify a 'G' ('General' - aka 'P', 'Psychopathology') factor, summarising a parsimonious structure of general psychopathology, have been carried out since Guttman's notion of a G factor of intelligence (Guttman, 1954). However, it was only at the end of the 1990s that this research was extended to general community samples, leading to the identification of two underlying latent factors, such as an internalised dimension of mood and anxiety symptoms and an externalised dimension of substance use and antisocial behaviour (Krueger *et al.*, 1998); an additional third dimension of thought disturbances further emerged when psychotic symptoms were included in these models (Markon and Krueger, 2006, Markon, 2010, Kotov *et al.*, 2011, Wright *et al.*, 2013). In the Dunedin study, Caspi et al interpreted a general factor as an individual's propensity to develop different forms of psychopathology (Caspi *et al.*, 2014), and a similar interpretation was given by the

Hierarchical Taxonomy Of Psychopathology (HiTOP) group (Kotov *et al.*, 2017). In the field of psychosis, a general factor was proposed to encompass a shared susceptibility encompassing enduring non-affective and affective psychotic disorders (Reininghaus *et al.*, 2013, Reininghaus *et al.*, 2016), and my findings extend this conceptualization to an incidence FEP sample, where the G factor statistically accounted for the co-variation of manic and delusional symptoms. On the other hand, the contribution of negative, depressive, and disorganization items was minimal. Hence, in my FEP sample, G would represent a common presentation in schizophrenia and bipolar disorder (using current diagnostic system language), however, its validity as a phenotype indexing a common genetic propensity to these two disorders is not confirmed by my findings.

7.3.3 Do symptom dimensions index neurodevelopmental impairment in psychosis?

The specific symptom dimensions at FEP emerged as key elements for scoring inter-individual differences due to sociodemographic determinants, cannabis use, and polygenic risk scores. A question concerning these findings is whether patients may be stratified according to neurodevelopmental trajectories. In particular, the source and timing of disruptions over the neurodevelopmental process may produce heterogenous phenotypes that do not overlap with traditional diagnostic categories, and these abnormalities may be indexed by transdiagnostic symptom dimensions, i.e. using a ‘symptom-developmental approach’. My findings show that prominent negative symptomatology is more common in men, in those not using cannabis, having an earlier age at onset and high SZ-PRS. Although, I did not directly investigate early abnormalities in neural networks and deficits in neuro and social

cognition, according to a developmental risk model of psychosis, children carrying early abnormalities in neural networks (due to genetics and/or medical events) may experience deficits in neuro- and social cognition and take on a trajectory of scholastic and social difficulties, resulting often in social isolation and deficits in emotional expression (Cannon *et al.*, 2002a). These difficulties, which may attract further adverse events such as bullying, are indeed identified as primary negative symptoms at FEP. Altered cognitive schema may further exacerbate paranoid interpretations of otherwise neutral stimuli and trigger an early psychosis onset (Howes and Murray, 2014).

My findings also show that prominent positive symptoms are more common in ethnic minorities and in those using cannabis, following a dose-response relationship, and they are also associated with high SZ-PRS. Overall, these characteristics may be associated with a late impairment in the neurodevelopmental timeline (childhood – adolescence), where disadvantageous familial or social context and use of drugs may trigger psychosis in those with a good premorbid functioning (Murray *et al.*, 2004).

7.3.4 What can we learn from cannabis-associated psychopathology at FEP?

My findings reported in Chapter 5 indicate that different patterns of cannabis use contribute to explaining symptom dimension variation at FEP. This study is novel as it takes into account the potency of cannabis which has increased worldwide.

As previously mentioned, my findings can be interpreted according to the theory that cannabis-associated psychosis follows a different neurodevelopmental trajectory compared with psychotic disorders not associated with cannabis use. Patients who use cannabis tend to have reduced negative symptoms, which allow them to get illicit

substances or to be part of a peer group that uses them. Furthermore, there is evidence that cannabis-associated psychosis has other characteristics that, as a whole, are strongly indicative of less early neurodevelopmental impairment, such as better premorbid functioning (Ferraro *et al.*, 2013), less neurological signs (Ruiz-Veguilla *et al.*, 2012), and better neuropsychological functioning (Yucel *et al.*, 2012). The interpretation that cannabis-associated developmental impairment may occur in a late stage of brain maturation is consistent with evidence from epidemiological, neuroimaging, and neurochemical examinations. These studies show that the effects of cannabis on the brain and risk of psychosis are higher if the exposure to cannabis occurs in adolescence (Bossong and Niesink, 2010). For example, the Dunedin study showed that individuals were at higher risk of cannabis-associated psychosis if their age of cannabis initiation was under 15 (Arseneault *et al.*, 2002), and these findings were replicated in the GAP study (Di Forti *et al.*, 2014). Similarly, some neuroimaging studies have claimed to find more global reduction in grey matter volume (Wilson *et al.*, 2000) as well as alterations in white matter (Zalesky *et al.*, 2012, Orr *et al.*, 2016) in individuals who started using cannabis in adolescence. Finally, positron emission tomography reports suggest that early initiation to cannabis use is correlated with lower dopamine synthesis capacity in the striatum (Urban *et al.*, 2012). Interestingly, low dopamine synthesis capacity is a characteristic that has been often reported in cannabis-associated psychosis (Urban *et al.*, 2012, Mizrahi *et al.*, 2013, Thompson *et al.*, 2013, Bloomfield *et al.*, 2014), as opposed to the pattern of a high dopamine synthesis in the striatum which is commonly seen in idiopathic schizophrenia (McCutcheon *et al.*, 2020). In cannabis-associated psychosis, it remains unclear whether the low release of pre-synaptic dopamine precedes cannabis use or it is a consequence of the regular use of

cannabis. It has been hypothesised that cannabis-associated dopaminergic abnormalities could be post-synaptic rather than pre-synaptic (Murray *et al.*, 2014), The possibility of different neurodevelopmental pathways resulting in different dopamine abnormalities is relevant for interpreting my findings on the relationship between use of cannabis and the positive dimensions of psychotic symptoms and experiences. While in patients and controls, the positive dimensions were associated with current use of cannabis, coherently with what is known about the short-term psychotropic effects of Δ9-THC (Hindley *et al.*, 2020), only in patients were positive symptoms associated with the extent of lifetime exposure to cannabis, following a dose-response pattern. This finding suggests that patients may be vulnerable to long-term effects of cannabis, perhaps elicited through a dysfunctional endocannabinoid system during adolescence (Bossong and Niesink, 2010), as demonstrated in animal models (Pistis *et al.*, 2004). In particular, the endocannabinoid system and exogenous cannabinoids may be involved in all steps of brain maturation, since this process is genetically determined, epigenetically driven, and environmentally influenced (Tau and Peterson, 2010). The endocannabinoid system has been widely reported as dysfunctional in psychosis (Volk and Lewis, 2016, Minichino *et al.*, 2019), and this may result in dysregulation of various neurodevelopmental processes, including synaptogenesis and neural pruning during adolescence and short- and long-term plasticity processes (Basavarajappa *et al.*, 2009).

7.3.4 Secondary prevention of cannabis-associated psychosis

Whether or not symptom presentation in cannabis-associated psychosis reflects a late developmental impairment in psychosis, symptom dimensions may be a

candidate target for secondary prevention strategies in cannabis-associated psychosis (Chapter 5). Currently, individuals presenting with cannabis-associated FEP usually receive the same treatment as patients with 'idiopathic' schizophrenia, despite differences clearly existing in the clinical presentation of these two groups. The absence of specific guidelines is a matter of urgency, considering that in South London, up to 21%, of new cases of psychosis can be attributed to daily use of cannabis, and up to 30% to the use of high-potency varieties (Di Forti *et al.*, 2019a). Moreover, approximately 35% of patients presenting with a cannabis-induced psychosis have a later transition to a diagnosis of schizophrenia (Murrie *et al.*, 2019). Since cannabis use is a preventable risk factor for the onset and a worse course of psychosis, it is urgent to develop treatment strategies based on the stratification of patients at FEP according to their symptom profile and patterns of cannabis use. These strategies should take into account that cannabis users keep having the most prominent positive symptomatology if they do not discontinue the use of cannabis after FEP (Schoeler *et al.*, 2016a). Moreover, cannabis cessation or reduction strategies should take into account that FEP patients using cannabis are often young and have good premorbid functioning. Using the most appropriate form of communication and treatment, this sub-group of patients may be receptive to the dissemination of credible and persuasive information on the detrimental effects of cannabis on mental health (Englund *et al.*, 2017, McClure *et al.*, 2019). Finally, the findings reported in my thesis support the caution that governments and policy makers should take before legalising cannabis for recreational use. There is a risk of cannabis use increasing in countries following such legalising policies (Melchior *et al.*, 2019, Murray and Hall, 2020), which may widely increase the distribution of positive psychotic symptomatology, both in cases and in the general population.

Finally, psychological interventions, which may be based on motivational enhancement therapy, family therapy, and contingency management could be offered, as recently recommended by the WHO (World Health Organization, 2020), and high-quality trials should be conducted to evaluate the effects of these interventions (Hunt *et al.*, 2019).

7.3.5 Towards personalised medicine?

In clinical practice, the identification of key features at FEP may be critical for improving the prediction of a long-term illness prognosis and tailoring personalised treatment from the beginning of the disease. From a research perspective, studies using predictive analysis at an individual-level are emerging in addition to the classic group-based studies (Hahn *et al.*, 2017). Although the classic group-based studies allow us to identify treatments that are effective for the average patient, they may jeopardise relevant information for smaller sub-group of patients. Hence, from a clinical perspective, it is crucial to integrate parameters from different modalities of investigation regardless of diagnostic categories, ranging from symptom dimensions to socio-environmental and biological determinants. In Figure 1, two possible clinical scenarios are described where a developmental-symptom approach may be useful to formulate clinical impressions, potentially guiding future research into personalised medicine (Figure 1). Indeed, biological parameters such as SZ-PRS may be useful in the future for formulating clinical impressions and informing clinical decisions.

However, general limitations should be considered in integrating PRS analysis into a symptom-developmental approach.

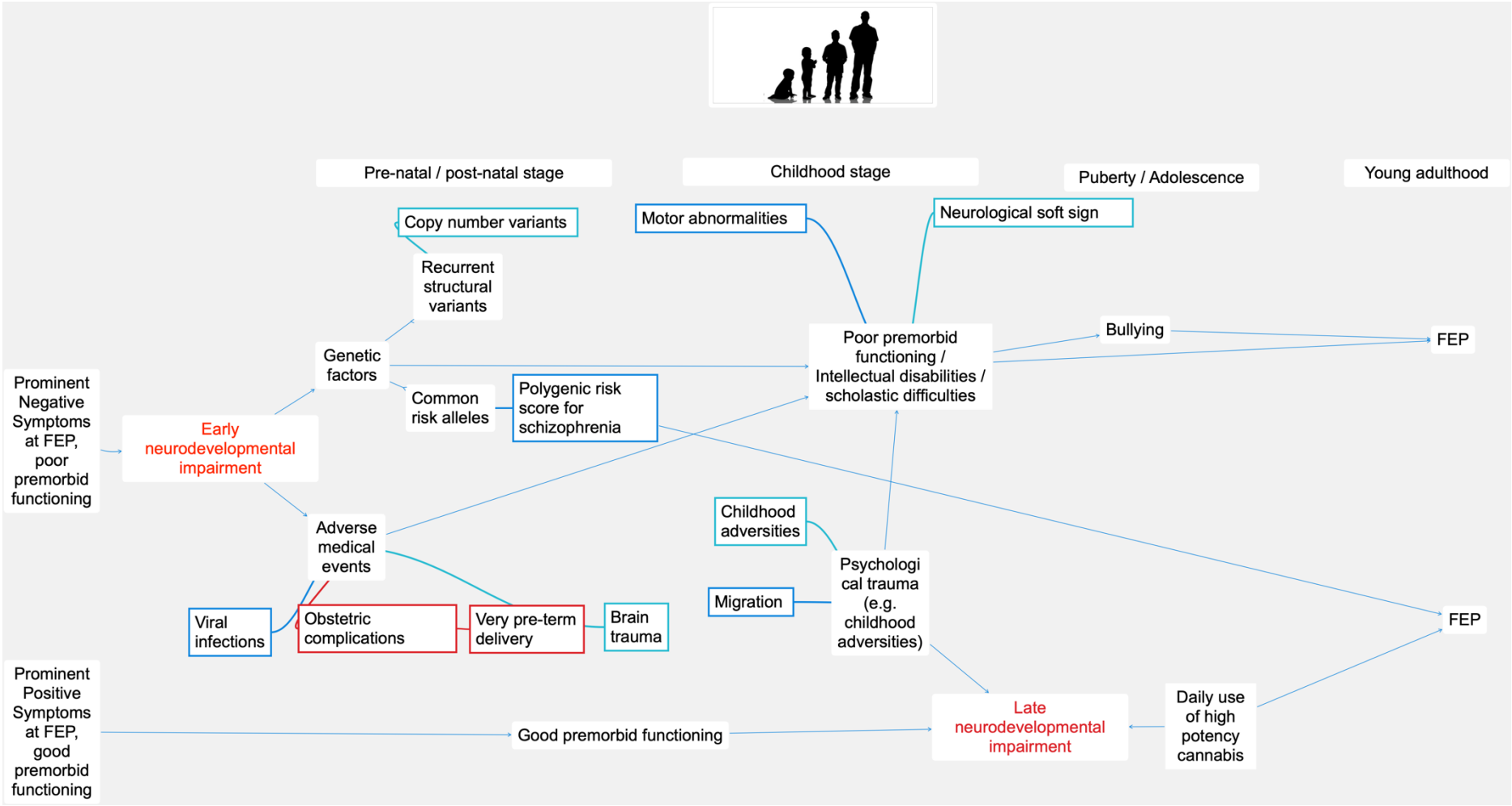
1) Missing heritability. Currently, only 22% of variance in SZ is explained by common genetic variance, resulting in a high degree of missing heritability. Further study efforts examining larger GWAS, rare variants, environmental modifiers, and epigenetic effects are needed to make personalised medicine effective in real clinical practice.
2) Lack of trans-ancestral studies. Currently, SZ GWAS is best powered for individuals of a European ancestry. This may require a researcher to restrict analysis to individuals of European ancestry, to better control population stratification. It is crucial to address this limitation as early as possible, conducting large SZ GWASs in different ethnic groups, to ensure that genetics does not increase disparities in the availability of care (Martin *et al.*, 2019).
3) Lack of symptom dimension GWASs. This is a common criticism in PGC GWASs, which lack clinical depth. The PGC highlighted that this was an intentional choice at the beginning of the Consortium activities, when it was agreed that diagnostic categories were the most appropriate phenotype characterization that would lead to the essential large sample size (Sullivan *et al.*, 2018), including for schizophrenia (Ripke *et al.*, 2013). However, now that a plateau has been reached on novel identified loci in relation to the progressive increase of sample size, new study designs may allow deeper phenotypic characterization.
4) Limited value in assisting with transition to psychosis, psychosis outcome, and pharmacotherapy. It has been proposed that SZ-PRS has the potential to improve the detection of at-risk individuals and their transition to psychosis (Oliver *et al.*, 2019). However, it has been shown that this strategy currently

would only marginally improve psychosis risk prediction (Perkins *et al.*, 2020). Moreover, in addition to SZ-PRS concerns, the use of the ultra-risk paradigm in clinical practice has been questioned as it would only intercept only a small proportion individuals destined to become actual FEP patients (Ajnakina *et al.*, 2017).

Moreover, SZ-PRS, currently, has poor predictive value on treatment-resistance (Legge *et al.*, 2019a), even if it has been associated with a more severe course of the disease (Jonas *et al.*, 2019). Finally, response to pharmacological therapy is known to be polygenic, and these genes may be different from the risk genes for the disorder (Garcia-Gonzalez *et al.*, 2017). An important finding in this field is the negative association between SZ-PRS and response to lithium (International Consortium on Lithium Genetics *et al.*, 2018). However, current pharmacogenetic testing for psychosis is still focused on single gene-drug interaction, with best level of evidence available for polymorphisms of *CYP2D6* and risperidone pharmacokinetic (Kneller *et al.*, 2020), *DRD2* and risperidone efficacy (Bousman, 2019), and *MC4R* and antipsychotic toxicity (Czerwensky *et al.*, 2013). Concerns have been raised due to the lack of standardization on these pharmacogenetics tests, and some authors have recommended that at least *CYP2D6*, *CYP2C19*, *HLA-A*, and *HLA-B* should be included in all gene panels to be used in pharmacogenetic testing (Bousman *et al.*, 2019).

5) Finally, conducting a PRS examination might require sharing the results with patients. This process may generate anxiety in an already vulnerable group who are predisposed to paranoia and only a small pilot study to date has examined these aspects (Putt *et al.*, 2020).

Fig. 2. Diagrams of two different neurodevelopmental pathways, that might be suggested by different observable symptom presentations at FEP



Explanatory note. In the first scenario, a patient would present with an onset of psychosis with prominent negative symptoms at FEP, poor premorbid functioning, and a high SZ-PRS. These factors would be suggestive of an early neurodevelopmental impairment; therefore, a careful investigation should be done in relation to psychiatric family history, the historical occurrence of pre- and peri-natal adverse events, and scholastic and premorbid functioning. Moreover, SZ-PRS and the other clinical characteristics, may help to detect individuals who are potentially CNV carriers, and suggest molecular diagnostics for recurrent structural genetic variants. This examination has already been proposed as a first line genetic test for patients with other neurodevelopmental conditions such as autism spectrum disorders, developmental delay, and intellectual disability (Schaefer et al., 2013, O'Byrne et al., 2016). Finally, since primary negative symptoms are a therapeutic challenge, from a clinical research perspective, more specific clinical trials should include patients with the indices of early neurodevelopmental impairment, as opposed to evaluating all patients experiencing both primary and secondary negative symptoms.

In a second scenario, a patient would present with a FEP with prominent positive symptoms, good premorbid functioning, and a history of daily use of high-potency cannabis. Here, information derived from SZ-PRS may be more unspecific, however in the future polygenic scores might be calculated with reference to specific biological pathways which may relate to the environmental risk factor, for example the endocannabinoid system. Meanwhile, environmental factors such as cannabis use may be preventable, and treatment strategies involving cannabis cessation measures should be applied, aiming to recover the pre-onset level of functioning and reduce the risk of a poor prognosis (Schoeler *et al.*, 2016a).

Chapter 8: Conclusive remarks and future directions

Clinicians and researchers are undergoing a crisis of confidence in psychiatric nosology. In response to the crisis, the findings from this PhD indicate that the bifactor model of psychopathology is a valid instrument toward conducting high-quality transdiagnostic research into psychosis. Cumulatively, these findings reinforce the case for integrating symptom dimension ratings into routine clinical practice, which would allow clinicians to formulate clinical impressions according to a developmental-symptom model, and to progressively develop personalised intervention schema. From this perspective, conditions such as cannabis-associated psychosis may benefit from developing specific secondary prevention strategies in early intervention services. Moreover, over the next years, the increasing predictive value of polygenic approaches may result in their application in clinical settings, further contributing to the paradigm shift from treating diagnoses toward treating the patient.

A number of future research directions have arisen from the work presented within this thesis, which are as follows:

Genetic variation of the endocannabinoid system and risk of first episode psychosis

First of all, the identification of a particular cannabis-associated symptomatology at FEP may imply the existence of a specific pathway toward developing cannabis-associated psychosis. However, the relationship between the use of exogenous cannabinoids and the polygenic variation of the endocannabinoids system with which they interact, has not been investigated yet. Hence, I have developed a pathway-

specific polygenic score, which indexes the genetic susceptibility to schizophrenia due to endocannabinoid genes only (Quattrone *et al.*, 2019).

Epigenetic pattern of transdiagnostic symptom dimensions at first episode psychosis

Secondly, symptom dimensions can be further validated with additional biological determinants, such as epigenome data. This will allow me to conduct the first epigenome-wide association study on symptom dimensions with genome-wide methylation data using the EPIC array on about 1,000 participants in the EU-GEI study.

Longitudinal stability of transdiagnostic symptom dimensions and their relationship with psychosis outcome

Thirdly, to further validate the bifactor structure, the longitudinal stability of the bifactor structure of psychopathology and its relationship with outcome measures should be evaluated. During my PhD, I have led a follow-up study of around 300 FEP patients and 100 controls from the EU-GEI and the GAP sample, on average five years after their onset of psychosis, which will enable me to assess the stability of the bifactor structure psychopathology at follow up.

Finally, I hope this thesis and its future developments will encourage consideration toward symptom dimensions in formulating clinical impressions and toward conducting more hypotheses-driven transdiagnostic research into psychosis.

In summary, this PhD thesis has shown that symptom dimensions are valid and useful phenotypes in the field of psychosis. This work highlights that these

dimensions may be integrated with biological and socio-environmental risk determinants, allowing to examine relevant clinical questions. As genetics move from research to clinical application, these enhanced phenotypes have the potential to contribute to an accurate individual characterization.

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